

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
21 July 2005 (21.07.2005)

PCT

(10) International Publication Number  
**WO 2005/065646 A2**

(51) International Patent Classification<sup>7</sup>: **A61K 9/00**

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(21) International Application Number:  
PCT/US2004/043929

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(22) International Filing Date:  
28 December 2004 (28.12.2004)

(81) Designated States (*unless otherwise indicated, for every  
kind of national protection available*): AE, AG, AL, AM,  
AT, AU, AZ, BA, BB, BG, BR, BW, BY, BZ, CA, CH, CN,  
CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI,  
GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE,  
KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD,  
MG, MK, MN, MW, MX, MZ, NA, NI, NO, NZ, OM, PG,  
PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, SY, TJ, TM,  
TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM,  
ZW.

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
60/533,112 29 December 2003 (29.12.2003) US

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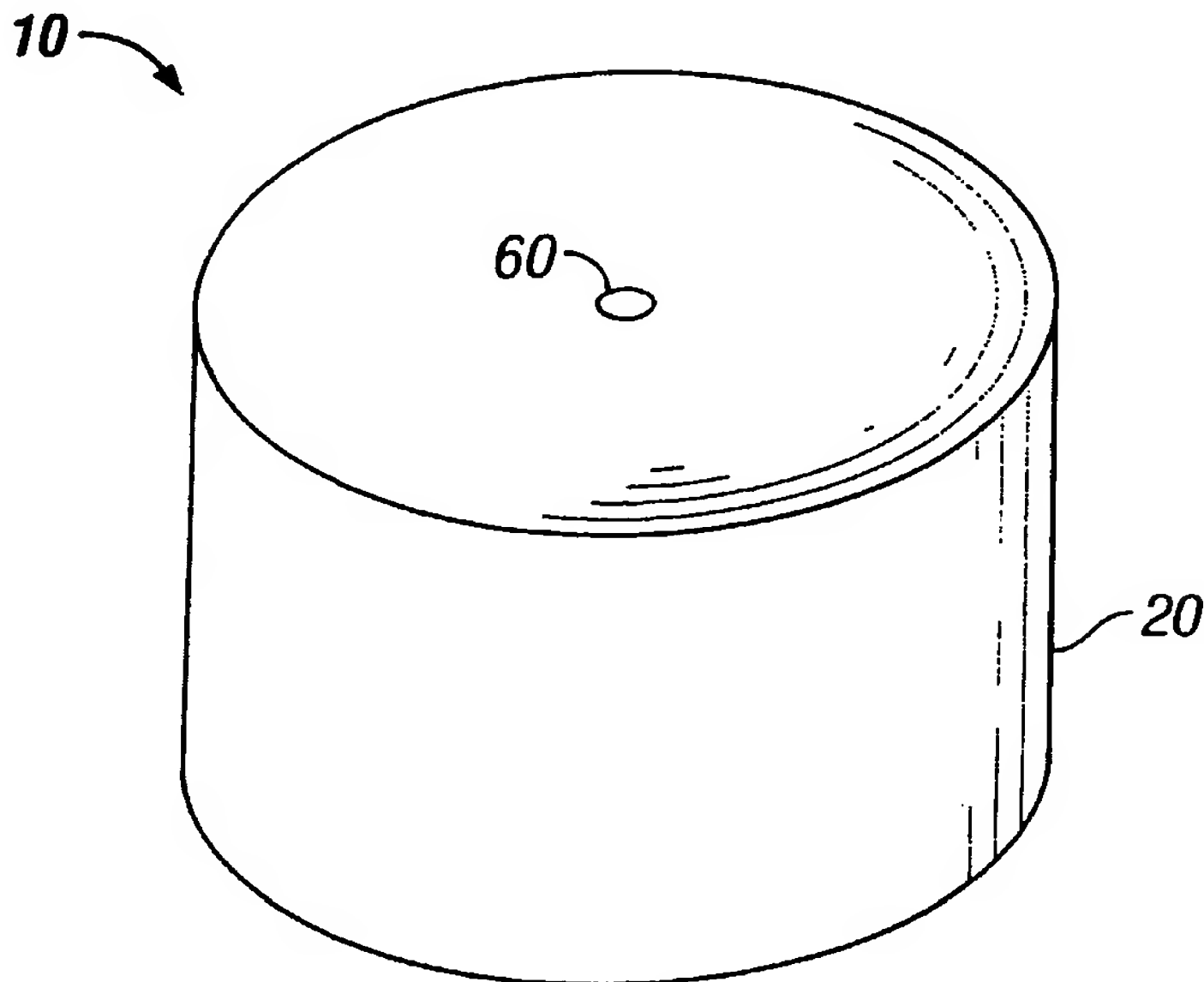
(84) Designated States (*unless otherwise indicated, for every  
kind of regional protection available*): ARIPO (BW, GH,  
GM, KE, LS, MW, MZ, NA, SD, SL, SZ, TZ, UG, ZM,  
ZW), Eurasian (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM),  
European (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI,  
FR, GB, GR, HU, IE, IS, IT, LT, LU, MC, NL, PL, PT, RO,  
SE, SI, SK, TR), OAPI (BF, BJ, CF, CG, CI, CM, GA, GN,  
GQ, GW, ML, MR, NE, SN, TD, TG).

Published:

— *without international search report and to be republished  
upon receipt of that report*

[Continued on next page]

(54) Title: NOVEL DRUG COMPOSITIONS AND DOSAGE FORMS



(57) Abstract: The present invention is directed to novel drug compositions and dosage forms compris-  
ing said drug compositions. The drug compositions  
of the present invention comprise a pharmaceutical  
agent and a solubilizing agent. The drug composi-  
tions of the present invention are particularly advan-  
tageous for use with low solubility and/or low dis-  
solution rate pharmaceutical agents. The present in-  
vention is further directed to methods for manufac-  
turing of said drug compositions and dosage forms.  
The present invention is further directed to methods  
of treatment comprising administration of said drug  
compositions and dosage forms.



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## NOVEL DRUG COMPOSITIONS AND DOSAGE FORMS

### CROSS REFERENCE TO RELATED APPLICATION

This application claims the benefit of U. S. Provisional Application  
5 60/533,112, filed on December 29, 2003, which is incorporated by reference  
herein in its entirety.

### FIELD OF THE INVENTION

**[0001]** The present invention is directed to novel drug compositions  
10 comprising a pharmaceutical agent and a solubilizing agent. The drug  
compositions of the present invention are particularly advantageous for use  
with low solubility and / or low dissolution rate pharmaceutical agents. The  
present invention is further directed to dosage forms containing said drug  
compositions. The present invention is further directed to methods for the  
15 preparation of the drug compositions and dosage forms of the present  
invention. The present invention is further directed to methods of treatment  
comprising administering, to a subject in need thereof, the drug compositions  
and / or dosage forms of the present invention.

### BACKGROUND OF THE INVENTION

**[0002]** Topiramate, a fructopyranose sulfamate derivative, also known  
as 2,3:4,5-bis-O-(1-methylethylidene)- $\beta$ -D-fructopyranose sulfamate, (more  
fully disclosed in US Patent No. No.4,513,006) has been demonstrated in  
clinical trials of human epilepsy to be effective as adjunctive therapy or as  
25 monotherapy in treating simple and complex partial seizures and secondarily  
generalized seizures (E. FAUGHT, B.J. WILDER, R.E. RAMSEY, R.A. REIFE,  
L D. KRAMER, G.W. PLEDGER, R.M. KARIM et. al., *Epilepsia* **1995**, 36 (S4),  
33; S.K. SACHDEO, R.C. SACHDEO, R.A. REIFE, P. LIM and G. PLEDGER,  
*Epilepsia* **1995**, 36 (S4), 33; T.A. GLAUSER, *Epilepsia* **1999**, 40 (S5), S71-80;  
30 R.C. SACHDEO, Clin. Pharmacokinet. **1998**, 34, 335-346), and is currently  
marketed for the treatment of seizures in patients with simple and complex  
partial epilepsy and seizures in patients with primary or secondary generalized

seizures in the United States, Europe and select other markets throughout the world for use as an anti-epileptic drug.

5     **[0003]**       Topiramate is a white crystalline powder that is soluble in alkaline solutions containing sodium hydroxide or sodium phosphate, soluble in acetone, dimethylsulfoxide and ethanol. However, the solubility of topiramate in water at room temperature is only about 9.8 mg/ml. Topiramate is not extensively metabolized and is excreted largely through the urine. Physicians' Desk Reference, Thompson Healthcare, 56<sup>th</sup> Ed., pp. 2590-2591 (2002).

10    **[0004]**       Topiramate pharmacokinetics are linear, producing a dose proportional increase in blood plasma concentration levels with increased dosing. Further, topiramate treatment has shown no evidence of patients developing drug tolerance with prolonged treatment over time. Following oral administration of an immediate release dosage form, topiramate is rapidly absorbed with peak plasma drug concentrations noted in approximately 2  
15    hours. The mean elimination half life is about 21 hours. Topiramate pharmacokinetics are also not significantly affected by food. For the treatment of epilepsy the recommended dosage of Topamax<sup>®</sup> is 400 mmg/day in one or multiple doses. Physicians' Desk Reference, Thompson Healthcare, 56<sup>th</sup> Ed., pp. 2590-2595 (2002). For the treatment of epilepsy in adults, treatment is  
20    initiated with a dose of 25-50mg/day, with the dosage titrated in dose increments of 25-50mg at weekly intervals to the recommended or effective dose.

25    **[0005]**       More recently, topiramate has been disclosed for the treatment of a variety of disorders including glaucoma and other ocular disorders (including diabetic retinopathy), essential tremor, restless limb syndrome, obesity, weight loss, Type II Diabetes Mellitus, Syndrome X, impaired oral glucose tolerance, diabetic skin lesions, cluster headaches, neuralgia, neuropathic pain (including diabetic neuropathy), elevated blood glucose levels, elevated blood pressure, elevated lipids, bipolar disorder, dementia, depression, psychosis, mania,  
30    anxiety, schizophrenia, obsessive compulsive disorder ("OCD"), post traumatic stress disorder ("PTSD"), attention deficit hyperactivity disorder ("ADHD"), impulse control disorders (including bulimia, binge eating, substance abuse, etc.), amyotrophic lateral sclerosis ("ALS"), asthma, autism, autoimmune



disorders (including psoriasis, rheumatoid arthritis, etc.), chronic neurodegenerative disorders, acute neurodegeneration, sleep apnea and other sleep disorders and wound healing.

5       **[0006]**       The art is replete with descriptions of dosage forms for sustained or controlled release of pharmaceutical agents. While a variety of sustained release dosage forms for delivering certain drugs may be known, not every drug may be suitably delivered from those dosage forms because of solubility, dissolution rate, metabolic processes, absorption and / or other physical, chemical and physiological parameters that are unique to the drug and / or the  
10       mode of delivery.

**[0007]**       Dosage forms that incorporate low solubility drugs, including high drug loading dosage forms, provide a major challenge for controlled release delivery technology as these systems tend to result in tablets or capsules of such large size that patients are unwilling or unable to swallow them.

15       **[0001]**       Dosage forms using surfactants are known in the art. Patent No. 6,569,463 describes using drug formulations consisting of coated granules, in which the coating consists of at least one surfactant and preferably a mixture of the surfactant with a hydrophobic drug and a lipophilic additive. This substrate coating facilitates rapid dispersion and provides rapid, sustained solubilization  
20       of the drug in the absence of liquid ingredients. The lipophilic additive further enhances solubilization of the drug or promotes dispersion *in vivo*.

**[0008]**       Pharmaceutical agents characterized as having low solubility and / or low dissolution rates are typically administered in multiple divided dosage forms, particularly at high dosage levels, for example at greater than or equal  
25       to about 100 mg / day. Thus conventional dosage forms of said low solubility and / or low dissolution rate pharmaceutical agents do not lend themselves to controlled or sustained therapy, particularly for once-a-day administration.

**[0009]**       Thus, there remains a need for a means to deliver low solubility and / or low dissolution rate pharmaceutical agents, for example topiramate,  
30       particularly at high dosage levels, with various delivery patterns, in dosage forms that are feasible and convenient for patients to swallow.

**[00010]**       More particularly, there remains a need for drug compositions and dosage forms comprising said drug compositions that provide dose-

regulated, preferably controlled release, therapy over a prolonged period of time with low solubility and / or low dissolution rate pharmaceutical agents.

The need also includes a need for effective dosing methods, dosage forms and devices that will permit the controlled release of topiramate or other low

5 solubility and / or low dissolution rate pharmaceutical agents over a prolonged period of time in order to increase the time between dosing, preferably to obtain a twice-a-day dosing regimen and most preferably to obtain a once-a-day dosing regimen. Such dosage forms should also have the capability of being formulated to deliver the drug composition in a substantially zero order  
10 rate of release, a substantially ascending rate of release, or in other hybrid release rates, as appropriate for the pharmaceutical agent being delivered.

**[00011]** Drug delivery devices (i.e. dosage forms) in which a drug composition is delivered as a slurry, suspension or solution from a small exit orifice by the action of an expandable layer are described in U.S. Patents Nos.  
15 5,633,011; 5,190,765; 5,252,338; 5,620,705; 4,931,285; 5,006,346; 5,024,842; and 5,160,743. Typical devices include a tablet comprising an expandable push layer and a drug layer, which tablet is surrounded by a semi-permeable membrane having an exit orifice. Such delivery systems, further minimize any effects related to the environment of use, for example the effects of localized  
20 stirring conditions on delivery performance. In certain instances, the tablet is provided with a subcoat to delay release of the drug composition to the environment of use.

**[00012]** Devices in which a drug composition is delivered in a dry state from a large exit orifice by the action of an expandable layer are described in  
25 US Patent Nos. 4,892,778, 4,915,949 and 4,940,465 and 5,023,088. The referenced patents describe a dispenser for delivering a beneficial agent to an environment of use that includes a semi-permeable wall containing a layer of expandable material that pushes a dry drug layer composition out of the compartment formed by the wall. The exit orifice in the device is substantially  
30 the same diameter as the inner diameter of the compartment formed by the wall. In such devices, a substantial area of the drug layer composition is exposed to the environment of use leading to release performance that can be subject to the stirring conditions in such environment.

**[00013]** While dosage forms which deliver the drug composition to the environment of use in the dry state through a large exit orifice may provide suitable release of drug over a prolonged period of time, the drug layer composition is however exposed to the environment of use over a large surface area. This exposure may lead to release performance characteristics that are affected by the conditions within such environment. More specifically, the exposure of the drug layer to the variably turbulent fluid environment of use such as the upper gastrointestinal tract may result in agitation-dependent release of drug that in some circumstances is difficult to control. Moreover, such dosage forms delivering in the dry state into a semisolid environment lacking sufficient volumes of bulk water, such as in the lower colonic environment of the gastrointestinal tract, may have difficulty liberating the dry dispensed drug composition into the environment as the high solids content composition tends to adhere to the dosage form at the site of the large orifice. Accordingly, it may be advantageous to release the drug as a well hydrated slurry or suspension that may be metered by control of rate of expansion of the push layer in combination with the smaller size of the exit orifice in the dosage form to minimize effects of localized stirring conditions on delivery performance.

**[00014]** US Pat. Nos. 5,938,654; 4,957,494; 5,023,088; 5,110,597; 5,340,590; 4,824,675; and 5,391,381 disclose drug delivery systems which deliver the drug substances by expelling discrete drug containing tablets at a controlled rate over time.

**[00015]** Still other devices incorporate liquid drug formulations that are released at a controlled rate over time. These devices are disclosed in US Pat. Nos. 4,111,201; 5,324,280; and 6,174,547. However, such liquid osmotic delivery systems are limited in the concentration of drug in the liquid formulation and hence, the drug loading available. Thus for the delivery of high doses of low solubility drugs, these delivery systems may be of an unacceptably large size or number for therapeutic purposes.

**[00016]** Still other delivery systems utilize a liquid carrier to deliver tiny time pills suspended within the liquid carrier. Such devices are disclosed in US Pat. No. 4,853,229 and 4,961,932. These suspensions require that the

therapeutic dose of pharmaceutical agent be dispensed by volume with measuring devices such as graduated cylinders or measuring spoons, a dispensing process that can be messy and inconvenient for the patient to administer.

5     **[00017]**       The dosage forms described above deliver pharmaceutical agents at an approximately zero order rate of release (i.e. wherein the rate of release of the drug substance as a function of time is approximately constant).

10     Recently, dosage forms have been disclosed for delivering drugs at substantially ascending rates of release, such as ALZA Corporation's Concerta<sup>®</sup> methylphenidate product, as disclosed in PCT Published Application Nos. US 99/11920 (WO 99/62496); US 97/13816 (WO 98/06380); and US 97/16599 (WO 98/14168). These dosage forms involve the use of multiple drug layers with sequentially increasing concentrations of drug in each drug layer to produce the substantially ascending rate of release of the drug over  
15     time. While such multi-layer tablet constructions represent a significant advancement to the art, these devices also have limited capability of delivering low solubility pharmaceutical agents, particularly at relatively large doses, as they may result in tablets or capsules of a size that patients are unwilling or unable to swallow.

20     **[00018]**       More recently, Cutler, N., in US Publication US 2003/0072802 A1 published April 17, 2003, discloses sustained release formulations of topiramate for the treatment of bipolar disorder, mania and depression.

25     **[00019]**       Almarsson et al., in US Patent 6,559,293 B1 (PCT Publication WO 2003/70738) disclose novel topiramate salts and pharmaceutically compositions thereof.

### **SUMMARY OF THE INVENTION**

30     **[00020]**       The present invention is directed to a drug composition comprising a pharmaceutical agent and a solubilizing agent, wherein the pharmaceutical agent is selected from a low solubility pharmaceutical agent or a low dissolution rate pharmaceutical agent, and wherein the pharmaceutical agent comprises greater than 11% by weight of the drug composition.

**[00021]** The present invention is further directed to a drug composition comprising topiramate and solubiliizing agent.

**[00022]** The present invention is further directed to a dosage form comprising any of the drug compositions described herein.

5 **[00023]** The present invention is further directed to a dosage form comprising a core comprising any of the drug compositions described herein and a push layer comprising an osmopolymer; a semi-permeable wall surrounding the core and an exit orifice through the semi-permeable wall for releasing the drug composition from the dosage form, preferably over a  
10 prolonged period of time.

**[00024]** The present invention is further directed to a dosage form comprising a core comprising a first drug composition, a second drug composition and a push layer comprising an osmopolymer; a semi-permeable wall surrounding the core and an exit orifice through the semi-permeable wall  
15 for releasing the drug composition from the dosage form, preferably over a prolonged period of time.

**[00025]** The present invention is further directed to a dosage form comprising

(a) a core comprising a first drug composition, a second drug  
20 composition and a push layer comprising an osmopolymer;  
(b) a semi-permeable wall surrounding the core; and  
(c) an exit orifice through the semi-permeable wall for releasing the drug compositions from the dosage form over a prolonged period of time;

wherein the first drug composition comprises a first pharmaceutical  
25 agent and a first solubilizing agent, wherein the first pharmaceutical agent is selected from a low solubility pharmaceutical agent or a low dissolution rate pharmaceutical agent; and

wherein the second drug composition comprises a second  
pharmaceutical agent and a second solubilizing agent, wherein the second  
30 pharmaceutical agent is selected from a low solubility pharmaceutical agent or a low dissolution rate pharmaceutical agent, and wherein the pharmaceutical agent comprises greater than 11% by weight of the second drug composition.  
In one embodiment of the present invention, the first pharmaceutical agent and



the second pharmaceutical agent are the same and the amount of the first pharmaceutical agent in the first drug composition is less than the amount of the second pharmaceutical agent in the second drug composition. In another embodiment, the first pharmaceutical agent and the second pharmaceutical agent are the same and the concentration of the first pharmaceutical agent in the first drug composition is less than the concentration of the second pharmaceutical agent in the second drug composition. In the dosage forms of the present invention, the first solubilizing agent and the second solubilizing agent can be the same or different, preferably, the first solubilizing agent and the second solubilizing agent are the same.

**[00026]** The present invention is further directed to a dosage form which provide a substantially zero order rate of release or a substantially ascending rate of release. The present invention is further directed to a dosage form which provides a release rate which results in a substantially ascending drug plasma concentration.

**[00027]** The present invention is further directed to a method for the preparation of any of the drug compositions and / or dosage forms described herein.

**[00028]** The present invention is further directed to a method of treating a disorder selected from the group consisting of epilepsy, migraine, glaucoma, ocular disorders, diabetic retinopathy, essential tremor, restless limb syndrome, obesity, weight loss, Type II Diabetes Mellitus, Syndrome X, impaired oral glucose tolerance, diabetic skin lesions, cluster headaches, neuralgia, neuropathic pain, diabetic neuropathy, elevated blood glucose levels, elevated blood pressure, elevated lipids, bipolar disorder, dementia, depression, psychosis, mania, anxiety, schizophrenia, OCD, PTSD, ADHD, impulse control disorders, ALS, asthma, autism, autoimmune disorders, chronic neurodegenerative disorders, acute neurodegeneration, sleep apnea and sleep disorders or promoting wound healing comprising administering to a subject in need thereof any of the drug compositions and / or dosage forms described herein.



**BRIEF DESCRIPTION OF THE FIGURES**

[00029] The following figures are not drawn to scale, and are set forth to illustrate various embodiments of the invention.

5 [00030] Figure 1 illustrates an embodiment of an osmotic dosage form of the present invention, illustrating the dosage form prior to administration to a subject.

[00031] Figure 2 illustrates the dosage form of Figure 1 in opened section, illustrating a single internally housed drug composition.

10 [00032] Figure 3 illustrates the dosage form of Figure 1 in opened section view, illustrating a bi-layer comprising a drug composition and a separate and contacting push layer for pushing the drug composition from the dosage form.

[00033] Figure 4 illustrates the dosage form of Figure 1, which further comprising an immediate release external overcoat of pharmaceutical agent on the dosage form.

15 [00034] Figure 5 illustrates an opened view of another embodiment of the dosage form of the present invention illustrating a tri-layer arrangement comprising two drug compositions in parallel arrangement and a separate and contacting push layer for pushing the drug layers from the capsule shaped dosage form.

20 [00035] Figure 6 illustrates the solubility of topiramate in aqueous solutions of different surfactants (having different HLB values), at different surfactant concentration. This figure further represents a method of selecting a surfactant for use with topiramate, comprising measuring the effect of different concentrations of surfactants and / or of different types of surfactants on drug  
25 solubility.

[00036] Figures 7, 8, 9 and 10 illustrate release patterns of topiramate from osmotic dosage forms as described in more detail with the Examples which follow herein.

30 [00037] Figure 11 illustrates the release pattern for an osmotic dosage form comprising 12.5 mg topiramate.

[00038] Figures 12 and 13 illustrate release patterns for osmotic dosage forms comprising 100 mg topiramate and exhibiting a substantially zero order rate of release and substantially ascending rate of release, respectively.

[00039] Figures 14, 15 and 16 illustrate release patterns for osmotic dosage forms comprising topiramate, each exhibiting a substantially ascending rates of release.

5 [00040] In the drawing figures and specification, like parts in related figures are identified by like numbers. The terms appearing earlier in the specification and in the description of the drawing figures, as well as embodiments thereof, are further described elsewhere in the disclosure.

#### DETAILED DESCRIPTION OF THE INVENTION

10 [00041] The present invention is best understood by reference to the following definitions, the drawings and exemplary disclosure provided herein.

[00042] The expressions "**exit**" and "**exit orifice**" shall mean an opening in a dosage form which permits drug to exit the dosage form. Suitable examples include, but are not limited to, a passageway; an aperture; an orifice; and a bore. The expressions also include an orifice that is formed or formable from a substance or polymer that erodes, dissolves or is leached from the outer wall to thereby form an exit orifice.

[00043] By "**dosage form**" is meant a pharmaceutical composition or device capable of delivering a pharmaceutical agent. Suitable examples of dosage forms include, but are not limited to tablets, capsules, gel-caps, matrix forms, osmotic forms, immediate release forms, controlled release forms, sustained release forms, extended release forms, and the like.

[00044] As used herein, unless otherwise noted, the terms "**drug composition**" shall mean a formulation comprising at least one pharmaceutical agent. Preferably, the drug composition comprises a pharmaceutical agent and a solubilizing agent, preferably, a surfactant, more preferably a solubilizing surfactant. More preferably, the drug composition comprises a pharmaceutical agent, a solubilizing agent, preferably, a surfactant and a structural polymer. The drug composition may further optionally contain one or more inactive ingredients, i.e., pharmaceutically acceptable excipients such as disintegrants, binders, diluents, lubricants, stabilizers, antioxidants, osmotic agents, colorants, plasticizers, coatings and the like.

**[00045]** As used herein, unless otherwise noted, the term **"push layer"** shall mean a formulation which does not contain pharmaceutical agent and which comprises an osmopolymer. Preferably, the push layer comprises an osmopolymer and an osmoagent. The push layer may further optionally contain one or more inactive ingredients, for example disintegrants, binders, diluents, lubricants, stabilizers, antioxidants, osmotic agents, colorants, plasticizers, coatings and the like.

**[00046]** As used herein, unless otherwise noted, the terms **"pharmaceutical agent"** and **"drug"** shall mean a pharmaceutical agent, drug, compound, pharmaceutically acceptable salt, prodrug or derivative thereof. Preferably, the pharmaceutical agent or drug is a low solubility and / or low dissolution rate pharmaceutical agent. More preferably, the pharmaceutical agent is topiramate.

**[00047]** As used herein, unless otherwise noted, the term **"pharmaceutically acceptable salt"**, shall mean any salt whose anion or cation does not contribute significantly to the toxicity or pharmacological activity of the salt, and, as such, they are the pharmacological equivalents of the acids or bases of the compound. Suitable pharmaceutically acceptable salts include acid addition salts which may, for example, be formed by reacting the drug compound with a suitable pharmaceutically acceptable acid such as hydrochloric acid, sulfuric acid, fumaric acid, maleic acid, succinic acid, acetic acid, benzoic acid, citric acid, tartaric acid, carbonic acid or phosphoric acid; and base addition salts, including alkali metal salts, e.g., sodium or potassium salts; alkaline earth metal salts, e.g., calcium or magnesium salts; and salts formed with suitable organic ligands, e.g., quaternary ammonium salts, which may be similarly prepared by reacting the drug compound with a suitable pharmaceutically acceptable base.

**[00048]** Thus, representative pharmaceutically acceptable salts include, but are not limited to, the following: acetate, benzenesulfonate, benzoate, bicarbonate, bisulfate, bitartrate, borate, bromide, calcium edetate, camsylate, carbonate, chloride, clavulanate, citrate, dihydrochloride, edetate, edisylate, estolate, esylate, fumarate, gluceptate, gluconate, glutamate, glycolylarsanilate, hexylresorcinate, hydrabamine, hydrobromide,

hydrochloride, hydroxynaphthoate, iodide, isothionate, lactate, lactobionate, laurate, malate, maleate, mandelate, mesylate, methylbromide, methylnitrate, methylsulfate, mucate, napsylate, nitrate, N-methylglucamine ammonium salt, oleate, pamoate (embonate), palmitate, pantothenate, phosphate/diphosphate, polygalacturonate, salicylate, stearate, sulfate, subacetate, succinate, tannate, tartrate, teoclate, tosylate, triethiodide and valerate.

**[00049]** Representative acids and bases which may be used in the preparation of pharmaceutically acceptable salts include the following: acids including acetic acid, 2,2-dichloroacetic acid, acylated amino acids, adipic acid, alginic acid, ascorbic acid, L-aspartic acid, benzenesulfonic acid, benzoic acid, 4-acetamidobenzoic acid, (+)-camphoric acid, camphorsulfonic acid, (+)-(1S)-camphor-10-sulfonic acid, capric acid, caproic acid, caprylic acid, cinnamic acid, citric acid, cyclamic acid, dodecylsulfuric acid, ethane-1,2-disulfonic acid, ethanesulfonic acid, 2-hydroxy-ethanesulfonic acid, formic acid, fumaric acid, galactaric acid, gentisic acid, glucoheptonic acid, D-gluconic acid, D-glucuronic acid, L-glutamic acid,  $\alpha$ -oxo-glutaric acid, glycolic acid, hipuric acid, hydrobromic acid, hydrochloric acid, (+)-L-lactic acid, ( $\pm$ )-DL-lactic acid, lactobionic acid, maleic acid, (-)-L-malic acid, malonic acid, ( $\pm$ )-DL-mandelic acid, methanesulfonic acid, naphthalene-2-sulfonic acid, naphthalene-1,5-disulfonic acid, 1-hydroxy-2-naphthoic acid, nicotinic acid, nitric acid, oleic acid, orotic acid, oxalic acid, palmitric acid, pamoic acid, phosphoric acid, L-pyroglutamic acid, salicylic acid, 4-amino-salicylic acid, sebaic acid, stearic acid, succinic acid, sulfuric acid, tannic acid, (+)-L-tartaric acid, thiocyanic acid, p-toluenesulfonic acid and undecylenic acid; and bases including ammonia, L-arginine, benethamine, benzathine, calcium hydroxide, choline, deanol, diethanolamine, diethylamine, 2-(diethylamino)-ethanol, ethanolamine, ethylenediamine, N-methyl-glucamine, hydrabamine, 1H-imidazole, L-lysine, magnesium hydroxide, 4-(2-hydroxyethyl)-morpholine, piperazine, potassium hydroxide, 1-(2-hydroxyethyl)-pyrrolidine, secondary amine, sodium hydroxide, triethanolamine, tromethamine and zinc hydroxide.

**[00050]** As used herein the term "**low solubility**" shall mean that the neat pharmaceutical agent (in the absence of surfactants or other excipients) exhibits a solubility of less than about 100 mg/ml in de-ionized water at 37°C.

Preferably, low solubility shall mean a solubility of less than about 50 mg/ml, more preferably, less than about 25 mg/ml, more preferably still, less than about 15 mg/ml, more preferably still, less than about 10 mg/ml, more preferably still, less than about 5 mg/ml, most preferably, less than about 1 mg/ml.

**[00051]** As defined herein, the solubility of a pharmaceutical agent is determined by adding the pharmaceutical agent to stirred or agitated de-ionized water maintained in a constant temperature bath at a temperature of 37°C until no more pharmaceutical agent dissolves. The resulting solution saturated with the pharmaceutical agent is then filtered, typically under pressure through a 0.8-micron Millipore filter, and the concentration of the pharmaceutical agent in the solution is measured by any appropriate analytical method including gravimetric, ultraviolet spectrophotometry, chromatography, and the like. The solubility of the pharmaceutical agent is measured at equilibrium.

**[00052]** As used herein, the term "**low dissolution rate**" shall mean that rate of dissolution of the pharmaceutical agent under constant surface area (i.e. the rate at which the pharmaceutical agent dissolves in de-ionized water at 37°C) is between 0 mg/min/cm<sup>2</sup> and about 20 mg/min/cm<sup>2</sup>, preferably, between about 0.1 mg/min/cm<sup>2</sup> and about 10 mg/min/cm<sup>2</sup>, more preferably, between about 0.1 mg/min/cm<sup>2</sup> and about 5 mg/min/cm<sup>2</sup>, more preferably still, between about 0.1 mg/min/cm<sup>2</sup> and about 2 mg/min/cm<sup>2</sup>, more preferably still, between about 0.1 mg/min/cm<sup>2</sup> and about 1.5 mg/min/cm<sup>2</sup>, most preferably, between about 0.1 mg/min/cm<sup>2</sup> and about 1.25 mg/min/cm<sup>2</sup>.

**[00053]** As defined herein, the dissolution rate of a pharmaceutical agent is determined by the method as described in USP 26, NF21, p.2333.

**[00054]** Suitable examples of low solubility pharmaceutical agents (i.e. those with a solubility in de-ionized water at 37°C of less than about 100 mg/ml) include, but are not limited to itraconazole, loratadine, thioridazine, thiethylperazine, ketoconazole, terfenadine, tretinoin, methdilazine, buprenorphine, thiothixene, simvastatin, indomethacin, domperidone, erythromycin, vitamin B, levonorgestrel, lovastatin, nicardipine, diclofenac, chlorpromazine, estradiol, digitoxin, liothyronine, glyburide, droperidol,



verapamil, triazolam, fluocinonide, loxapine, prazepam, lindane, flurbiprofen, oxaprozin, progesterone, pimozide, methyclothiazide, ethinyl estradiol, finasteride, clozapine, haloperidol, diflunisal, prochlorperazine, warfarin, imipramine, felodipine, mefenamic acid, methotrimeprazine, ibuprofen, spironolactone, nimodipine, biperiden, perphenazine, fluphenazine, methyltestosterone, glipizide, disopyramide, methoxsalen, diazepam, penicillin, ketoprofen, nifedipine, etoposide, metolazone, digoxin, betamethasone, fluoxymesterone, nabumetone, reserpine, furosemide, sulfadiazine, nitrendipine, nitrofurantoin, lorazepam, triamcinolone, omeprazole, dexamethasone, doxorubicin, clonazepam, bendroflumethiazide, chlorthalidone, methylprednisolone, pyrimethamine, flumazenil, tetracaine, fludrocortisone, quinidine, morphine, temazepam, oxazepam, epinephrine, fentanyl, cefazolin, prednisolone, tetracycline, chlorpropamide, chlorothiazide, azathioprine, prednisone, hydrocortisone, nystatin, phenazopyridine, trimethoprim, fenfluramine, isosorbide dinitrate, allopurinol, sulfamethoxazole, doxycycline, hydrochlorothiazide, amphotericin B, diphenoxylate, trichlormethiazide, zidovudine, famotidine, and the like.

**[00055]** Preferably, the low solubility pharmaceutical agent is other than (is not) phenytoin. Preferably, the low solubility pharmaceutical agent is other than phenytoin and carbamazepine. Preferably, the low solubility pharmaceutical agent is other than phenytoin, mephenytoin, phenobarbital, primidone, carbamazepine, ethosuximide, methsuximide, phensuximide, trimethadione, clonazepam, clorazepate, phenacemide, paramethadione, primaclone, clobazam, felbamate, flunarizine, lamotrigine, progabide, vibabatim, eterobarb, gabapentin, oxcarbazepine, ralitoline, tiagobine, sulthiame and tioridone.

**[00056]** The low solubility and / or low dissolution rate pharmaceutical agents may be incorporated into the drug composition and / or dosage forms of the present invention in amounts in the range of from about 1 milligram to about 750 milligrams, preferably in the range of from about 5 mg to about 250 mg, more preferably in the range of from about 10 mg to about 250 mg.



[00057] An "immediate-release dosage form" refers to a dosage form that releases greater than or equal to about 80% of the pharmaceutical agent in less than or equal to about 1 hour.

[00058] By "sustained release" is meant continuous release of a pharmaceutical agent over a prolonged period of time.

[00059] By "controlled release" is meant continuous release of a pharmaceutical agent over a prolonged period of time, wherein the pharmaceutical agent is released at a controlled rate over a controlled period of time.

[00060] By "prolonged period of time" is meant a continuous period of time of greater than about 1 hour, preferably, greater than about 4 hours, more preferably, greater than about 8 hours, more preferably greater than about 10 hours, more preferably still, greater than about 14 hours, most preferably, greater than about 14 hours and up to about 24 hours.

[00061] As used herein, unless otherwise noted, "rate of release" or "release rate" of a drug refers to the quantity of drug released from a dosage form per unit time, e.g., milligrams of drug released per hour (mg/hr). Drug release rates for dosage forms are typically measured as an *in vitro* rate of drug release, i.e., a quantity of drug released from the dosage form per unit time measured under appropriate conditions and in a suitable fluid.

[00062] The release rates referred to herein are determined by placing a dosage form to be tested in de-ionized water in metal coil or metal cage sample holders attached to a USP Type VII bath indexer in a constant temperature water bath at 37°C. Aliquots of the release rate solutions, collected at pre-set intervals, are then injected into a chromatographic system fitted with an ultraviolet or refractive index detector to quantify the amounts of drug released during the testing intervals.

[00063] As used herein a drug release rate obtained at a specified time refers to the *in vitro* release rate obtained at the specified time following implementation of the release rate test. The time at which a specified percentage of the drug within a dosage form has been released from said dosage form is referred to as the " $T_x$ " value, where "x" is the percent of drug that has been released. For example, a commonly used reference

measurement for evaluating drug release from dosage forms is the time at which 70% of drug within the dosage form has been released. This measurement is referred to as the " $T_{70}$ " for the dosage form. Preferably,  $T_{70}$  is greater than or equal to about 8 hours, more preferably,  $T_{70}$  is greater than or equal to about 12 hours, more preferably still,  $T_{70}$  is greater than to equal to about 16 hours, most preferably,  $T_{70}$  is greater than or equal to about 20 hours. Preferably,  $T_{70}$  is less than about 24 hours, more preferably,  $T_{70}$  is less than about 20 hours.

[00064] By "**C**" is meant the concentration of drug in blood plasma, or serum, of a subject, generally expressed as mass per unit volume, typically nanograms per milliliter. For convenience, this concentration may be referred to herein as "**drug plasma concentration**", "**plasma drug concentration**" or "**plasma concentration**", which is intended to be inclusive of a drug concentration measured in any appropriate body fluid or tissue. The plasma drug concentration at any time following drug administration is referenced as  $C_{\text{time}}$ , as in  $C_{9h}$  or  $C_{24h}$ , etc.

[00065] As used herein, "**steady state**" when used in describing the drug plasma concentration of a pharmaceutical agent, shall mean a plasma drug concentration in the range of from about 5 ng/ml to about 500 ng/ml, preferably, from about 25 ng/ml to about 250 ng/ml, with the proviso that during the 24 hour period after administration the quotient formed by  $[C_{\text{max}} - C_{\text{min}}]/C_{\text{avg}}$  (i.e. the variation in the blood plasma concentration of the drug) is about 3 or less, preferably, about 2 or less, more preferably, about 1 or less.

[00066] Persons of skill in the art will appreciate that blood plasma drug concentrations obtained in individual subjects will vary due to interpatient variability in the many parameters affecting drug absorption, distribution, metabolism and excretion. For this reason, unless otherwise indicated, when a drug plasma concentration is listed, the value listed is the calculated mean value based on values obtained from a groups of subjects tested.

[00067] As used herein, unless otherwise noted, the term "**zero order rate of release**" shall mean a rate of release wherein the amount of drug released as a function of time is substantially constant. More particularly, the rate of release of drug as a function of time shall vary by less than about 30%,

preferably, less than about 20%, more preferably, less than about 10%, most preferably, less than about 5%, wherein the measurement is taken over the period of time wherein the cumulative release is between about 25% and about 75%, preferably, between about 25% and about 90%.

5     **[00068]**     As used herein unless otherwise noted, the term “**ascending rate of release**” shall mean a rate of release wherein the amount of drug released as a function of time increases over a period of time, preferably continuously and gradually. Preferably, the rate of drug released as a function of time increases in a steady (rather than step-wise) manner. More preferably, an  
10     ascending rate of release may be characterized as follows. The rate of release as a function of time for a dosage form is measured and plotted as % drug release versus time or as milligrams of drug released / hour versus time. An ascending rate of release is characterized by an average rate (expressed in mg of drug per hour) wherein the rate within a given two hour span is higher as  
15     compared with the previous two hour time span, over the period of time of about 2 hours to about 12 hours, preferably, about 2 hours to about 18 hours, more preferably about 4 hours to about 12 hours, more preferably still, about 4 hours to about 18 hours. Preferably, the increase in average rate is gradual such that less than about 30% of the dose is delivered during any 2 hour  
20     interval, more preferably, less than about 25% of the dose is delivered during any 2 hour interval. Preferably, the ascending release rate is maintained until at least about 50%, more preferably until at least about 75% of the drug in the dosage form has been released.

25     **[00069]**     One skilled in the art will recognize that as the increase in the area under the curve increases (e.g from 1% to 10%), the total time over which the drug is released from the dosage form will necessarily decrease and as such the determination of ascending rate of release will span a shorter overall period of time.

30     **[00070]**     As used herein, the term or “**ascending drug plasma concentration**” shall mean a drug plasma concentration profile over about the first 24 hours following initial dosing, wherein the profile shows an increase to a maximum concentration, wherein said maximum occurs more than about 6

hours following the initial dose, preferably, more than about 8 hours following initial dose, more preferably, more than about 12 hours after dose.

5     **[00071]**       When referring to a drug composition, "**high dosage**" shall mean a drug composition wherein the pharmaceutical agent, preferably topiramate, is present in an amount greater than or equal to about 20%, preferably greater than or equal to about 30%, more preferably greater than or equal to about 40%, by weight of the total drug composition.

10    **[00072]**       When referring to a dosage form, "**high dosage**" shall mean a dosage form wherein the pharmaceutical agent, preferably topiramate, is present in an amount greater than or equal to about 20%, preferably greater than or equal to about 30%, more preferably greater than or equal to about 40%, by weight of the drug compositions within the dosage form.

15    **[00073]**       As used herein, the term "**therapeutically effective amount**" shall mean that amount of pharmaceutical agent that elicits the biological or medicinal response in a tissue system, animal or human that is being sought by a researcher, veterinarian, medical doctor or other clinician, which includes alleviation of the symptoms of the disease or disorder being treated.

20    **[00074]**       The term "**subject**" as used herein, refers to an animal, preferably, a mammal, most preferably, a human, who has been the object of treatment, observation or experiment.

25    **[00075]**       As used herein, unless otherwise noted, the term "**structural polymer**" shall mean any component, for example a polymer or sugar, which is capable of water absorption and which may increase the viscosity of the drug compositions and / or may impart osmotic activity to the drug composition and / or may act as a suspending agent for the drug composition. Suitable examples of structural polymers include, but are not limited to poly(alkyleneoxide polymers of between 100,000 and 750,000 molecular weight, including polyethylene oxide (such as POLYOX<sup>®</sup> N80; POLYOX<sup>®</sup> N10, POLYOX N750, and the like); polymethylene oxide, polybutylene oxide and polyhexylene oxide, 30    and poly(carboxymethylcellulose) of 40,000 to 400,000 number average molecular weight, represented by poly(alkali carboxymethylcellulose), poly(sodium carboxymethylcellulose), poly(potassium carboxymethylcellulose), poly(lithium carboxymethylcellulose), and the like. Suitable example also

include, but are not limited to sugars such as maltodextrins (such as MALTRIN M040, MALTRIN M100, MALTRIN M150, MALTRIN M200, MALTRIN M250, and the like); sugars comprising lactose, glucose, raffinose, sucrose, mannitol, sorbitol and the like. Suitable examples also include, but are not limited to  
5 polyvinylpyrrolidone (PVP) (such as PVPs of grades 12PF or K2932, and the like); hydroxypropylcellulose; hydroxy propyl alkylcellulose of 9200 to 125,000 average molecular weight represented by hydroxypropyl ethylcellulose, hydroxypropyl methylcellulose, hydroxypropyl butylcellulose, hydroxypropyl pentylcellulose, and the like; polyvinyl pyrrolisone vinyl acetate co-olymers; and  
10 poly(vinylpyrrolidone) of upto 1,000,000 average molecular weight. Preferably, the structural polymer is a polyethyleneoxide polymers of between 100,000 and 300,000 molecular weight. More preferably, the structural polymer is POLYOX® N80.

**[00076]** Preferably, the structural polymer is selected from MALTRIN M100, POLYOX N10 and POLYOX N80, more preferably, the structural  
15 polymer is POLYOX N80.

**[00077]** As used herein, unless otherwise noted, the term “**solubilizing agent**” shall mean any component which increases the solubility and / or dissolution rate of a pharmaceutical agent. Preferably, the solubilizing agent is  
20 a surfactant. Suitable examples of solubilizing agents include, but are not limited to polyethylene glycol (PEG) 3350, polyethylene glycol 8K, and surfactants including, but not limited to, KOLLIDON K90, KOLLIDON 12PF, KOLLIDON 17PF, KOLLIDON 25/30; LUTROL F68, LUTROL F87, LUTROL F127, LUTROL F108; MYRJ 52, MYRJ 53; PVP K2939, and the like.

25 Additional preferred surfactants include, but are not limited to, sorbitan monopalmitate, sorbitan monostearate, glycerol monostearate, polyoxyethylene stearate, sucrose cocoate, polyoxyethylene 40 sorbitol lanolin derivative, polyoxyethylene 75 sorbitol lanolin derivative, polyoxyethylene 6 sorbitol beeswax derivative, polyoxyethylene 20 sorbitol beeswax derivative,  
30 polyoxyethylene 20 sorbitol lanolin derivative, polyoxyethylene 50 sorbitol lanolin derivative, polyoxyethylene 23 lauryl ether, polyoxyethylene 23 lauryl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 2 cetyl ether with butylated hydroxyanisole and citric acid



added as preservatives, polyoxyethylene 2 stearyl ether, polyoxyethylene 21 stearyl ether, polyoxyethylene 100 stearyl ether, polyoxyethylene 10 cetyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 20 cetyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 2 stearyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 10 stearyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 20 stearyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 21 stearyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 20 oleyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 40 stearate, polyoxyethylene 50 stearate, polyoxyethylene 100 stearate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, polyoxyethylene 4 sorbitan monostearate, polyoxyethylene 20 sorbitan tristearate

**[00078]** More preferably, the solubilizing agent is a surfactant selected from the group of co-polymers of ethylene oxide and propylene oxide conforming to the general formula  $\text{OH}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})\text{H}$ . More preferably still, the surfactant is selected from the group consisting of LUTROL F68, LUTROL F87, LUTROL 108, LUTROL F127, MYRJ 52, MYRJ 53; most preferably, the surfactant is LUTROL F127.

**[00079]** As used herein, unless otherwise noted, the term “osmopolymer” shall mean a swellable, hydrophilic polymer that interacts with water and swells or expands to a high degree, typically exhibiting a 2-50 fold volume increase. Suitable examples, include but are not limited to poly(alkylene oxide) of 1 million to 15 million number-average molecular weight, as represented by poly(ethylene oxide), poly(alkali carboxymethylcellulose) of 500,000 to 3,500,000 number-average molecular weight, wherein the alkali is sodium, potassium or lithium; polymers that form hydrogels, such as CARBOPOL<sup>®</sup> acidic carboxypolymer, a polymer of acrylic cross-linked with a polyallyl sucrose, also known as carboxypolymethylene, and carboxyvinyl polymer having a molecular weight of 250,000 to 4,000,000; CYANAMER<sup>®</sup> polyacrylamides; cross-linked water swellable indenemaleic



anhydride polymers; GOOD-RITE<sup>®</sup> polyacrylic acid having a molecular weight of 80,000 to 200,000; AQUA-KEEPS<sup>®</sup> acrylate polymer polysaccharides composed of condensed glucose units, such as diester cross-linked polygluran; and the like.

5     **[00080]**     As used herein, unless otherwise noted, the terms “osmoagent” and “osmotically active agent” shall mean an agent which exhibits an osmotic activity gradient across a semi-permeable membrane. Suitable osmoagents include, but are not limited to, sodium chloride, potassium chloride, lithium chloride, magnesium sulfate, magnesium chloride, potassium sulfate, sodium  
10     sulfate, lithium sulfate, potassium acid phosphate, mannitol, urea, inositol, magnesium succinate, tartaric acid, raffinose, sucrose, glucose, lactose, sorbitol, inorganic salts, organic salts, carbohydrates, and the like.

15     **[00081]**     Preferred surfactant and structural polymer chemical and commercial / tradenames may be used interchangeably throughout the specification herein. For clarity the following is a listing of said surfactant and structural polymer chemical and corresponding commercial / tradenames.

Chemical Name	Tradename(s)
Poloxamer 188	PLURONIC <sup>®</sup> F68 = LUTROL <sup>®</sup> F68
Poloxamer 237	PLURONIC <sup>®</sup> F87 = LUTROL <sup>®</sup> F87
Poloxamer 338	PLURONIC <sup>®</sup> F108 = LUTROL <sup>®</sup> F108
Poloxamer 407	PLURONIC <sup>®</sup> F127 = LUTROL <sup>®</sup> F127
Polyoxyl 40 stearate	MYRJ <sup>®</sup> 52
Polyoxyl 50 stearate	MYRJ <sup>®</sup> 53
Polyethylene oxide of 100,000 molecular weight	POLYOX <sup>®</sup> N10
Polyethylene oxide of 200,000 molecular weight	POLYOX <sup>®</sup> N80
Polyethylene oxide of 300,000 molecular weight	POLYOX <sup>®</sup> N 750
Polyethylene oxide of 1,000,000 molecular weight	POLYOX <sup>®</sup> N 12K

Polyethylene oxide of 2,000,000 molecular weight	POLYOX <sup>®</sup> N 60K
Polyethylene oxide of 7,000,000 molecular weight	POLYOX <sup>®</sup> 303

**[00082]** The present invention is directed to a drug composition comprising a pharmaceutical agent and a solubilizing agent, wherein the pharmaceutical agent is selected from a low solubility pharmaceutical agent or a low dissolution rate pharmaceutical agent, wherein the pharmaceutical agent comprises greater than 11% by weight of the drug composition, wherein the solubilizing agent is a surfactant, and wherein the surfactant comprises greater than about 10% by weight of the drug composition.

**[00083]** The present invention is directed to a drug composition comprising a pharmaceutical agent and a solubilizing agent, wherein the pharmaceutical agent is selected from a low solubility pharmaceutical agent or a low dissolution rate pharmaceutical agent, wherein the pharmaceutical agent comprises greater than 11% by weight of the drug composition and wherein the solubilizing agent is a surfactant.

**[00084]** In an embodiment of the present invention is a drug composition comprising a pharmaceutical agent, a solubilizing agent and a structural polymer, wherein the pharmaceutical agent is selected from a low solubility pharmaceutical agent or a low dissolution rate pharmaceutical agent, and wherein the pharmaceutical agent comprises greater than 11% by weight of the drug composition.

**[00085]** The present invention is further directed to a drug composition comprising topiramate and a solubilizing agent. In an embodiment of the present invention, the topiramate comprises greater than 11% by weight of the drug composition. In another embodiment of the present invention is a drug composition comprising topiramate, a solubilizing agent and a structural polymer. Preferably, the solubilizing agent is a surfactant. Preferably, the solubilizing agent comprises greater than about 10% by weight of the drug composition.

5      **[00086]**      In an embodiment of the present invention is a drug composition comprising topiramate and a solubilizing agent, wherein the topiramate comprises greater than 11% by weight of the drug composition, wherein the solubilizing agent is a surfactant, and wherein the surfactant comprises greater than about 10% by weight of the drug composition.

10      **[00087]**      In an embodiment of the present invention is a drug composition, wherein the pharmaceutical agent, preferably topiramate, comprises greater than about 20% by weight of the drug composition. Preferably, the pharmaceutical agent, preferably topiramate, comprises greater than about 30% by weight of the drug composition, more preferably, the pharmaceutical agent, preferably topiramate, comprises greater than about 40% by weight of the drug composition.

15      **[00088]**      In another embodiment of the present invention is a drug composition, wherein the pharmaceutical agent, preferably topiramate, comprises between about 25% and about 55% by weight of the drug composition. Preferably, the pharmaceutical agent, preferably topiramate, comprises between about 30% and about 45% by weight of the drug composition.

20      **[00089]**      In an embodiment of the present invention is a drug composition, wherein the solubilizing agent is a surfactant. In another embodiment of the present invention is a drug composition, wherein the solubilizing agent, preferably surfactant, comprises about 10% by weight of the drug composition, preferably, about 20% by weight of the drug composition, more preferably, about 30% by weight of the drug composition, most preferably, about 40% by weight of the drug composition.

25      **[00090]**      In another embodiment of the present invention is a drug composition, wherein the solubilizing agent, preferably a surfactant, comprises between about 35% and about 55% by weight of the drug composition. Preferably, the solubilizing agent, preferably surfactant, comprises between about 40% and about 50% by weight of the drug composition.

30      **[00091]**      In an embodiment of the present invention, the solubilizing agent is present in an amount greater than about 5%, more preferably, in an amount greater than about 10%, more preferably still, in an amount greater than about

17.5%, more preferably still, in an amount greater than about 25%, more preferably still, in an amount greater than about 30%, more preferably still, in an amount greater than about 40%, more preferably still, in an amount greater than about 42.5%, more preferably still, in an amount greater than about 45%.

5     **[00092]**       In another embodiment of the present invention is a drug composition further comprising a structural polymer. Preferably, the structural polymer comprises between about 1% and about 90% by weight of the drug composition, preferably, the structural polymer comprises between about 5% and about 85% by weight of the drug composition, more preferably, the  
10    structural polymer comprises between about 5% and about 75% by weight of the drug composition, more preferably, the structural polymer comprises between about 10% and about 40% by weight of the drug composition. In an embodiment of the present invention, the structural polymer comprises between about 0% and about 90% by weight of the drug composition.

15    **[00093]**       The present invention is further directed to a dosage form comprising any of the drug compositions described herein. In an embodiment of the present invention is a dosage form comprising a drug composition, wherein the drug composition comprises topiramate and a solubilizing agent.

20    **[00094]**       In an embodiment of the present invention, the dosage form is a matrix form. In another embodiment of the present invention, the dosage form is an osmotic dosage form. In another embodiment of the present invention, the dosage form is a controlled release dosage form. Preferably, the dosage form is a controlled release, osmotic dosage form, preferably for oral administration.

25    **[00095]**       In an embodiment of the present invention is a dosage form comprising a drug composition as described herein, wherein the pharmaceutical agent is present in an amount in the range of about 1 milligram to about 750 milligrams, preferably about 5 milligrams to about 250  
30    milligramns, more preferably about 10 milligrams to about 250 milligrams. In another embodiment of the present invention is a dosage form comprising two drug compositions as described herein, wherein the sum of the amount of pharmaceutical agent present within the drug compositions is in the range of about 1 milligram to about 750 milligrams, preferably about 5 milligrams to

about 250 milligramns, more preferably about 10 milligrams to about 250 milligrams.

**[00096]** In another embodiment of the present invention is a dosage form comprising a drug composition, wherein the drug composition comprises  
5 topiramate, and a solubilizing agent, and wherein the topiramate is present in an amount in the range of about 1 milligram to about 750 milligrams, preferably about 5 milligrams to about 250 milligrams, more preferably about 10 milligrams to about 250 milligrams, more preferably still, the pharmaceutical agent is present in an amount selected from 10 mg, 20 mg, 40 mg, 45 mg, 80  
10 mg, 90 mg, 120 mg, 135 mg, 160 mg, 180 mg or 200 mg.

**[00097]** In another embodiment of the present invention is a dosage form comprising two drug compositions, wherein each drug composition comprises topiramate and an independently selected solubilizing agent, preferably surfactant, and wherein the sum of the amount of topiramate with the drug  
15 compositions is in the range of about 1 milligram to about 750 milligrams, preferably about 5 milligrams to about 250 milligramns, more preferably about 10 milligrams to about 250 milligrams, more preferably still, the pharmaceutical agent is present in an amount selected from 10 mg, 20 mg, 40 mg, 45 mg, 80 mg, 90 mg, 120 mg, 135 mg, 160 mg, 180 mg or 200 mg.

**[00098]** In an embodiment of the present invention is a dosage form comprising

(a) a core comprising a first drug composition and a push layer comprising an osmopolymer;

(b) a semi-permeable wall surrounding the core; and

25 (c) an exit orifice through the semi-permeable wall for releasing the drug compositions from the dosage form over a prolonged period of time.

**[00099]** In another embodiment of the present invention is a dosage form comprising

(a) a core comprising a first drug composition, a second drug composition  
30 and a push layer comprising an osmopolymer;

(b) a semi-permeable wall surrounding the core; and

(c) an exit orifice through the semi-permeable wall for releasing the drug compositions from the dosage form over a prolonged period of time.



**[000100]** In another embodiment of the present invention is a dosage form comprising

(a) a core comprising a first drug composition, a second drug composition and a push layer, wherein the first and second drug compositions comprise  
5 topiramate and independently selected solubilizing agents;

(b) a semi-permeable wall surrounding the core; and

(c) an exit orifice through the semi-permeable wall for releasing the drug compositions from the dosage form over a prolonged period of time.

**[000101]** In an embodiment of the present invention, is a dosage form  
10 comprising:

(a) a core comprising a first drug composition, a second drug composition and a push layer comprising an osmopolymer;

(b) a semi-permeable wall surrounding the core; and

(c) an exit orifice through the semi-permeable wall for releasing the first  
15 drug composition and the second drug composition from the dosage form over a prolonged period of time; wherein the first drug composition comprises between about 25% and about 40% by weight of topiramate and between about 25% and about 50% by weight of a surfactant; and the second drug composition comprises between about 30% and about 50% by weight of  
20 topiramate and between about 45% and about 60% by weight of a surfactant.

**[000102]** In another embodiment of the present invention is a dosage form comprising

(a) a core comprising

a first drug composition comprising a pharmaceutical agent and a  
25 solubilizing agent wherein the pharmaceutical agent is selected from a low solubility pharmaceutical agent or a low dissolution rate pharmaceutical agent, preferably topiramate, wherein the pharmaceutical agent comprises greater than 11% by weight of the drug composition, wherein the solubilizing agent is a surfactant, and wherein  
30 the surfactant comprises greater than about 10% by weight of the drug composition;

a second drug composition comprising a pharmaceutical agent and a solubilizing agent wherein the pharmaceutical agent is selected



from a low solubility pharmaceutical agent or a low dissolution rate pharmaceutical agent, wherein the pharmaceutical agent comprises greater than 11% by weight of the drug composition, wherein the solubilizing agent is a surfactant, and wherein the surfactant comprises greater than about 10% by weight of the drug composition; and  
5 a push layer,

(b) a semi-permeable wall surrounding the core; and

(c) an exit orifice through the semi-permeable wall for releasing the drug compositions from the dosage form over a prolonged period of time

10 **[000103]** In an embodiment of the present invention, the pharmaceutical agent and solubilizing agent in the first and second drug compositions are independently selected. Preferably, the pharmaceutical agent in the first and second drug compositions is the same, more preferably, the pharmaceutical agent in the first and second drug compositions is topiramate.

15 **[000104]** In an embodiment of the present invention, the amount and / or concentration of the pharmaceutical agent, preferably topiramate, within the first drug composition is less than the amount and / or concentration of the pharmaceutical agent, preferably topiramate, within the second drug composition.

20 **[000105]** In another embodiment of the present invention is a dosage form comprising

(a) a core comprising a first drug composition, a second drug composition and a push layer comprising an osmopolymer;

(b) a semi-permeable wall surrounding the core; and

25 (c) an exit orifice through the semi-permeable wall for releasing the first drug composition and the second drug composition from the dosage form over a prolonged period of time;

wherein the first drug composition comprises between about 25% and about 40% by weight of topiramate and between about 35% and about 50% by  
30 weight of a surfactant, and the second drug composition comprises between about 30% and about 40% by weight of topiramate and between about 45% and 55% by weight of a surfactant.

**[000106]** In another embodiment of the present invention is a dosage form comprising

(a) a core comprising a first drug composition, a second drug composition and a push layer comprising an osmopolymer;

5 (b) a semi-permeable wall surrounding the core; and

(c) an exit orifice through the semi-permeable wall for releasing the first drug composition and the second drug composition from the dosage form over a prolonged period of time; wherein the first drug composition comprises between about 5% and about 25% by weight of topiramate and between about 1% and 35% by weight of a surfactant, and the second drug composition comprises between about 10% and about 25% by weight of topiramate and between about 10% and 35% by weight of a surfactant.

**[000107]** In an embodiment of the present invention, the push layer comprises an osmopolymer. In another embodiment of the present invention, the push layer comprises an osmopolymer and an osmoagent.

**[000108]** In an embodiment of the present invention, the dosage form releases drug over a prolonged period of time, preferably over greater than 4 hours, more preferably, over greater than about 8 hours, more preferably still, over greater than about 10 hours, most preferably, over greater than about 14 hours. In another embodiment of the present invention, the dosage form releases drug over a prolonged period of time greater than about 14 hours and up to about 24 hours.

**[000109]** In an embodiment of the present invention, the dosage form releases drug with a substantially ascending rate of release. In another embodiment of the present invention, the dosage form releases drug with a substantially ascending rate of release. In yet another embodiment of the present invention, the dosage form releases drug at a rate which results in a substantially ascending drug plasma concentration.

**[000110]** In an embodiment of the present is a drug composition comprising topiramate, a surfactant, preferably LUTROL F127 and a structural polymer, preferably POLYOX N80; wherein the topiramate comprises about 5% by weight of the drug composition, wherein the surfactant comprises about

2% by weight of the drug composition, and wherein the structural polymer comprises about 88.7% by weight of the drug composition.

5     **[000111]**     In an embodiment of the present is a drug composition comprising topiramate, a surfactant, preferably LUTROL F127 and a structural polymer, preferably POLYOX N80; wherein the topiramate comprises about 12% by weight of the drug composition, wherein the surfactant comprises about 12% by weight of the drug composition, and wherein the structural polymer comprises about 71.7% by weight of the drug composition.

10     **[000112]**     In an embodiment of the present is a drug composition comprising topiramate, a surfactant, preferably LUTROL F127 and a structural polymer, preferably POLYOX N80; wherein the topiramate comprises about 32% by weight of the drug composition, wherein the surfactant comprises about 42% by weight of the drug composition, and wherein the structural polymer comprises about 16.5% by weight of the drug composition.

15     **[000113]**     In an embodiment of the present is a drug composition comprising topiramate, and a surfactant, preferably LUTROL F127; wherein the topiramate comprises about 43% by weight of the drug composition, and wherein the surfactant comprises about 49.9% by weight of the drug composition.

20     **[000114]**     In an embodiment of the present invention, the drug composition further comprises between about 10% and about 35% by weight of a structural polymer, and the second drug composition further comprises between about 0% and about 10% by weight of a structural polymer.

25     **[000115]**     In an embodiment of the present invention, the drug composition comprised between about 25% and about 35% by weight of topiramate, between about 25% and about 35% by weight of the surfactant, and between about 25% and about 35% by weight of the structural polymer.

30     **[000116]**     In an embodiment of the present invention, the drug composition comprised about 30% by weight of topiramate, about 29% by weight of the surfactant, and about 33% by weight of the structural polymer.

**[000117]**     In an embodiment of the present invention, the drug composition comprised between about 35% and about 45% by weight of topiramate,

between about 50% and about 60% by weight of the surfactant, and between about 0% and about 5% by weight of the structural polymer.

5     **[000118]**     In an embodiment of the present invention, the drug composition comprised about 37% by weight of topiramate, about 55% by weight of the surfactant, and about 0% by weight of the structural polymer.

**[000119]**     In an embodiment of the present invention, the drug composition comprised between about 2% and about 8% by weight of topiramate, between about 5% and about 15% by weight of the surfactant, and between about 75% and about 85% by weight of a structural polymer.

10    **[000120]**     In an embodiment of the present invention, the drug composition comprised about 6% by weight of topiramate, about 10% by weight of the surfactant, and about 80% by weight of the structural polymer.

**[000121]**     In an embodiment of the present invention, the drug composition comprised between about 10% and about 15% by weight of topiramate,  
15    between about 10% and about 20% by weight of the surfactant, and between about 60% and about 75% by weight of the structural polymer.

**[000122]**     In an embodiment of the present invention, the drug composition comprised about 13% by weight of topiramate, about 15% by weight of the surfactant, and about 69% by weight of the structural polymer.

20    **[000123]**     In an embodiment of the present invention, the drug composition further comprises polyvinyl pyrrolidone, wherein the polyvinyl pyrrolidone comprises about 2% by weight of the drug composition; stearic acid, wherein the stearic acid comprises about 1% by weight of the drug composition;  
25    magnesium stearate, wherein the magnesium stearate comprises about 0.25% by weight of the drug composition; and butylated hydroxytoluene, wherein the butylated hydroxytoluene comprises about 0.02% by weight of the drug composition.

30    **[000124]**     In an embodiment of the present invention, the drug composition further comprises polyvinyl pyrrolidone, wherein the polyvinyl pyrrolidone comprises about 2% by weight of the drug composition; stearic acid, wherein the stearic acid comprises about 1% by weight of the drug composition;  
magnesium stearate, wherein the magnesium stearate comprises about 0.25% by weight of the drug composition; iron oxide, wherein the iron oxide comprises

about 0.01% by weight of the drug composition, and butylated hydroxytoluene, wherein the butylated hydroxytoluene comprises about 0.02% by weight of the drug composition.

5 [000125] In an embodiment of the present invention, the drug composition further comprises polyvinyl pyrrolidone, wherein the polyvinyl pyrrolidone comprises about 2% by weight of the drug composition; stearic acid, wherein the stearic acid comprises about 3% by weight of the drug composition; magnesium stearate, wherein the magnesium stearate comprises about 0.25% by weight of the drug composition; butylated hydroxytoluene, wherein the  
10 butylated hydroxytoluene comprises about 0.02% by weight of the drug composition, and methyl cellulose, wherein the methyl cellulose comprises about 3.0% by weight of the drug composition.

[000126] In an embodiment of the present invention, the drug composition further comprises polyvinyl pyrrolidone, wherein the polyvinyl pyrrolidone  
15 comprises about 2% by weight of the drug composition; stearic acid, wherein the stearic acid comprises about 3% by weight of the drug composition; magnesium stearate, wherein the magnesium stearate comprises about 0.25% by weight of the drug composition; ferric oxide, wherein the ferric oxide comprises about 0.08% by weight of the drug composition; butylated  
20 hydroxytoluene, wherein the butylated hydroxytoluene comprises about 0.02% by weight of the drug composition, and methyl cellulose, wherein the methyl cellulose comprises about 3% by weight of the drug composition.

[000127] In an embodiment of the present invention is a drug composition comprising topiramate, wherein the topiramate comprises about 5% by weight  
25 of the drug composition; surfactant, preferably LUTROL F127 wherein the surfactant comprises about 2% by weight of the drug composition; a structural polymer, preferably POLYOX N80 wherein the structural polymer comprises about 88.7% by weight of the drug composition; PVP, preferably PVP K29-32, wherein the PVP comprises about 3% by weight of the drug composition;  
30 stearic acid, wherein the stearic acid comprises about 1% by weight of the drug composition; magnesium stearate, wherein the magnesium stearate comprises about 0.25% by weight of the drug composition; and butylated hydroxytoluene



(BHT), wherein the BHT comprises about 0.02% by weight of the drug composition.

5     **[000128]**     In an embodiment of the present invention is a drug composition comprising topiramate, wherein the topiramate comprises about 12% by weight of the drug composition; surfactant, preferably LUTROL F127, wherein the surfactant comprises about 12% by weight of the drug composition; a structural polymer, preferably POLYOX N80, wherein the structural polymer comprises about 71.7% by weight of the drug composition; PVP, preferably PVP K29-32, wherein the PVP comprises about 3% by weight of the drug composition; 10     stearic acid, wherein the stearic acid comprises about 1% by weight of the drug composition; magnesium stearate, wherein the magnesium stearate comprises about 0.25% by weight of the drug composition; iron oxide, wherein the iron oxide comprises about 0.02% by weight of the drug composition, and BHT, wherein the BHT comprises about 0.02% by weight of the drug composition.

15     **[000129]**     In an embodiment of the present invention is a drug composition comprising topiramate, wherein the topiramate comprises about 32% by weight of the drug composition; surfactant, preferably LUTROL F127, wherein the surfactant comprises about 42% by weight of the drug composition; a structural polymer, preferably POLYOX N80, wherein the structural polymer comprises 20     about 16.5% by weight of the drug composition; PVP, preferably PVP K29-32, wherein the PVP comprises about 3% by weight of the drug composition; stearic acid, wherein the stearic acid comprises about 1% by weight of the drug composition; magnesium stearate, wherein the magnesium stearate comprises about 0.5% by weight of the drug composition; BHT, wherein the BHT 25     comprises about 0.02% by weight of the drug composition and methyl cellulose, wherein the methyl cellulose comprises about 2.5% by weight of the drug composition.

30     **[000130]**     In an embodiment of the present invention is a drug composition comprising topiramate, wherein the topiramate comprises about 43% by weight of the drug composition; surfactant, preferably LUTROL F127, wherein the surfactant comprises about 49.9% by weight of the drug composition; PVP, preferably PVP K29-32, wherein the PVP comprises about 3% by weight of the drug composition; stearic acid, wherein the stearic acid comprises about 1% by

weight of the drug composition; magnesium stearate, wherein the magnesium stearate comprises about 0.5% by weight of the drug composition; ferric oxide, wherein the ferric oxide comprises about 0.08% by weight of the drug composition; BHT, wherein the BHT comprises about 0.02% by weight of the drug composition and methyl cellulose, wherein the methyl cellulose comprises about 2.5% by weight of the drug composition.

**[000131]** In an embodiment of the present invention is a dosage form comprising (a) a core comprising a first drug composition comprising topiramate, a surfactant, preferably LUTROL F127 and a structural polymer, preferably POLYOX N80 wherein the topiramate comprises about 5% by weight of the drug composition, wherein the surfactant comprises about 2% by weight of the drug composition, and wherein the structural polymer comprises about 88.7% by weight of the drug composition; a second drug composition comprising topiramate, a surfactant, preferably LUTROL F127 and a structural polymer, preferably POLYOX N80 wherein the topiramate comprises about 12% by weight of the drug composition, wherein the surfactant comprises about 12% by weight of the drug composition, and wherein the structural polymer comprises about 71.7% by weight of the drug composition; and a push layer.

**[000132]** In another embodiment of the present invention is a dosage form comprising (a) a core comprising a first drug composition comprising topiramate, a surfactant, preferably LUTROL F127 and a structural polymer, preferably POLYOX N80; wherein the topiramate comprises about 32% by weight of the drug composition, wherein the surfactant comprises about 42% by weight of the drug composition, and wherein the structural polymer comprises about 16.5% by weight of the drug composition; a second drug composition comprising topiramate, and a surfactant, preferably LUTROL F127; wherein the topiramate comprises about 43% by weight of the drug composition, and wherein the surfactant comprises about 49.9% by weight of the drug composition; and a push layer.

**[000133]** In an embodiment of the present invention is a dosage form comprising (a) a core comprising

a first drug composition comprising topiramate, wherein the topiramate comprises about 5% by weight of the drug composition; surfactant, preferably LUTROL F127 wherein the surfactant comprises about 2% by weight of the drug composition; a structural polymer, preferably POLYOX N80, wherein the structural polymer comprises about 88.7% by weight of the drug composition; PVP, preferably PVP K29-32, wherein the PVP comprises about 3% by weight of the drug composition; stearic acid, wherein the stearic acid comprises about 1% by weight of the drug composition; magnesium stearate, wherein the magnesium stearate comprises about 0.25% by weight of the drug composition; and BHT, wherein the BHT comprises about 0.02% by weight of the drug composition;

a second drug composition comprising topiramate, wherein the topiramate comprises about 12% by weight of the drug composition; surfactant, preferably LUTROL F127 wherein the surfactant comprises about 12% by weight of the drug composition; a structural polymer, preferably POLYOX N80, wherein the structural polymer comprises about 71.7% by weight of the drug composition; PVP, preferably PVP K29-32, wherein the PVP comprises about 3% by weight of the drug composition; stearic acid, wherein the stearic acid comprises about 1% by weight of the drug composition; magnesium stearate, wherein the magnesium stearate comprises about 0.25% by weight of the drug composition; iron oxide, wherein the iron oxide comprises about 0.02% by weight of the drug composition, and BHT, wherein the BHT comprises about 0.02% by weight of the drug composition; and

a push layer comprising an osmopolymer;

(b) a semi-permeable wall surrounding said core; and

(c) an exit orifice through the semi-permeable wall for releasing the first drug composition and the second drug composition from the dosage form over a prolonged period of time

**[000134]** In another embodiment of the present invention is a dosage form comprising (a) a core comprising

a first drug composition comprising topiramate, wherein the topiramate comprises about 32% by weight of the drug composition; surfactant, preferably LUTROL F127, wherein the surfactant comprises about 42% by weight of the

drug composition; a structural polymer, preferably POLYOX N80, wherein the structural polymer comprises about 16.5% by weight of the drug composition; PVP, preferably PVP K29-32, wherein the PVP comprises about 3% by weight of the drug composition; stearic acid, wherein the stearic acid comprises about 1% by weight of the drug composition; magnesium stearate, wherein the magnesium stearate comprises about 0.5% by weight of the drug composition; BHT, wherein the BHT comprises about 0.02% by weight of the drug composition and methyl cellulose, wherein the methyl cellulose comprises about 2.5% by weight of the drug composition;

a second drug composition comprising topiramate, wherein the topiramate comprises about 43% by weight of the drug composition; surfactant, preferably LUTROL F127, wherein the surfactant comprises about 49.9% by weight of the drug composition; PVP, preferably PVP K29-32, wherein the PVP comprises about 3% by weight of the drug composition; stearic acid, wherein the stearic acid comprises about 1% by weight of the drug composition; magnesium stearate, wherein the magnesium stearate comprises about 0.5% by weight of the drug composition; ferric oxide, wherein the ferric oxide comprises about 0.08% by weight of the drug composition; BHT, wherein the BHT comprises about 0.02% by weight of the drug composition and methyl cellulose, wherein the methyl cellulose comprises about 2.5% by weight of the drug composition; and

a push layer comprising an osmopolymer;

(b) a semi-permeable wall surrounding said core; and

(c) an exit orifice through the semi-permeable wall for releasing

the first drug composition and the second drug composition from the dosage form over a prolonged period of time.

**[000135]** In an embodiment of the present invention is a method of treating a disorder selected from the group consisting of epilepsy, migraine, glaucoma and other ocular disorders (including diabetic retinopathy), essential tremor, restless limb syndrome, obesity, weight loss, Type II Diabetes Mellitus, Syndrome X, impaired oral glucose tolerance, diabetic skin lesions, cluster headaches, neuralgia, neuropathic pain (including diabetic neuropathy), elevated blood glucose levels, elevated blood pressure, elevated lipids, bipolar

disorder, dementia, depression, psychosis, mania, anxiety, schizophrenia, OCD, PTSD, ADHD, impulse control disorders (including bulimia, binge eating, substance abuse, etc.), ALS, asthma, autism, autoimmune disorders (including psoriasis, rheumatoid arthritis, etc.), chronic neurodegenerative disorders, acute neurodegeneration, sleep apnea and other sleep disorders and / or for promoting wound healing, comprising administering to a subject in need thereof, of any of the drug compositions or dosage forms described herein.

**[000136]** Preferably, the disorder is selected from the group consisting of epilepsy, migraine, diabetic retinopathy, diabetic neuropathy, diabetic skin lesions, obesity, weight loss, Type II Diabetes Mellitus, Syndrome X, impaired oral glucose tolerance, elevated blood glucose levels and elevated blood pressure.

**[000137]** There are many approaches to achieving sustained release or controlled release of drugs from oral dosage forms known in the art. These different approaches may include, but are not limited to, for example, diffusion systems such as reservoir devices and matrix devices, dissolution systems such as encapsulated dissolution systems (including, for example, "tiny time pills") and matrix dissolution systems, combination diffusion/dissolution systems and ion-exchange resin systems as described in Remington's Pharmaceutical Sciences, 18th ed., pp. 1682-1685, (1990). Pharmaceutical agent dosage forms that operate in accord with these other approaches are encompassed by the scope of the present invention to the extent that said dosage form comprise a pharmaceutical agent and a solubilizing agent and / or produce a substantially zero order rate of release, a substantially ascending rate of release or a rate of release which results in a substantially ascending drug plasma concentration.

**[000138]** Sustained release or controlled release dosage forms may be prepared as osmotic dosage forms. Osmotic dosage forms utilize osmotic pressure to generate a driving force for imbibing fluid into a compartment formed, at least in part, by a semi-permeable wall that permits free diffusion of water but not drug or other components. A significant advantage to osmotic systems is that operation is pH-independent and thus continues at the osmotically determined rate throughout an extended time period, even as the



dosage form transits the gastrointestinal tract and encounters differing microenvironments having significantly different pH values. A review of such dosage forms is found in Santus and Baker, "Osmotic drug delivery: a review of the patent literature," Journal of Controlled Release 35 (1995) 1-21,

5 incorporated in its entirety by reference herein. In particular, the following U.S. Patents, owned by the assignee of the present application, ALZA Corporation, directed to osmotic dosage forms: Nos. 3,845,770; 3,916,899; 3,995,631; 4,008,719; 4,111,202; 4,160,020; 4,327,725; 4,519,801; 4,578,075; 4,681,583; 5,019,397; and 5,156,850. Such osmotic dosage forms generally comprise a  
10 drug layer, an optional push layer, a semi-permeable membrane which encompasses the drug and push layers and one or more exit orifices.

**[000139]** In the aqueous environment of the gastrointestinal (GI) tract, water is imbibed through the semi-permeable membrane of the osmotic dosage form, at a controlled rate. This causes the push layer to swell and the  
15 drug composition(s) to hydrate and form viscous, but deformable, masses. The push layer expands against the drug composition(s), which are pushed out through the orifice. The drug composition(s) exit the system through the exit orifice in the membrane over prolonged periods of time as water from the gastrointestinal tract is imbibed into the delivery system. At the completion of  
20 drug release, the biologically inert components of the dosage form are eliminated as a tablet shell.

**[000140]** Figure 1 is a perspective view of one embodiment of a sustained release osmotic dosage form in a standard biconvex round shaped tablet. Dosage form 10 comprises a semi-permeable wall 20 that surrounds and  
25 encloses an internal compartment (not seen in Figure 1). The internal compartment comprises a drug composition comprising a pharmaceutical agent and a solubilizing agent. Semi-permeable wall 20 is provided with at least one exit orifice 60 for connecting the internal compartment with the exterior environment of use. Accordingly, following oral ingestion of dosage  
30 form 10, water is imbibed through semi-permeable wall 20 and the pharmaceutical agent / drug composition is released through exit 60.

**[000141]** While the geometrical embodiment in Figure 1 illustrates a standard biconvex round shaped tablet, the dosage forms of the present

invention may embrace other geometries including, a capsule shaped caplet, oval, triangular and other shapes designed for oral administration, including buccal or sublingual dosage forms.

**[000142]** Figure 2 is a cutaway view of Figure 1 showing internal

5 compartment 15 containing a single drug composition 30, wherein the drug composition comprises pharmaceutical agent 31 in an admixture with selected excipients. The excipients may be selected to increase the solubility of the drug composition 30 and / or to provide an osmotic activity gradient for driving fluid from an external environment through semi-permeable wall 20 for forming  
10 a deliverable drug composition upon imbibition of fluid and / or for other performance and / or manufacturing purposes.

**[000143]** In an embodiment, the present invention is directed to a drug composition 30, wherein the drug composition comprises at least one pharmaceutical agent 31, preferably one to two pharmaceutical agents, more  
15 preferably one pharmaceutical agent and a solubilizing agent 33. Preferably the pharmaceutical agent 31 is topiramate. Preferably, the solubilizing agent 33 is a surfactant.

**[000144]** Preferably, drug composition 30 comprises a pharmaceutical agent 31 and a solubilizing agent 33, wherein the pharmaceutical agent 31 is a  
20 low solubility and / or a low dissolution rate pharmaceutical agent. Preferably, the drug composition of the present invention comprises at least about 5%, more preferably, at least about 11%, more preferably, at least about 17.5%, more preferably, at least about 25%, more preferably, at least about 30%, more preferably, at least about 40%, more preferably, at least about 42%,  
25 more preferably, at least about 45%, solubilizing agent 33, by weight of the drug composition.

**[000145]** In another embodiment of the present invention, as shown in Figure 2, the drug composition comprises a pharmaceutical agent 31, a solubilizing agent 33 (represented by vertical dashes) and a structural polymer  
30 32 (represented by horizontal dashed lines).

**[000146]** Drug composition 30 excipients may further optionally include a lubricant 34 (represented by horizontal wavy lines), an osmotically active agent,

also known as an osmoagent 35 (represented by "X" symbols) and / or a suitable binder 36 (represented by large circles).

5 [000147] In operation, following oral ingestion of dosage form 10, the osmotic activity gradient across the semi-permeable wall 20 causes water of the gastrointestinal tract to be imbibed through the semi-permeable wall 20, thereby forming a deliverable drug composition, e.g., a solution or suspension or hydrogel, within the internal compartment. The deliverable drug composition is then released through the exit orifice 60 as water continues to enter the internal compartment. As release of the drug composition occurs, water  
10 continues to be imbibed thereby driving continued release. In this manner, drug is released in a sustained and continuous manner over an extended time period.

[000148] Figure 3 is a cutaway view of Figure 1 with an alternate embodiment of internal compartment 15, wherein the internal compartment  
15 comprises a bi-layer configuration. In this embodiment, internal compartment 15 contains a bi-layered compressed core having a first drug composition 30 and a push layer 40. Drug composition 30, as described above with reference to Figure 1 and 2, comprises a pharmaceutical agent and a solubilizing agent, in an admixture with further, optional excipients.

20 [000149] As is described in more detail below, the second component, push layer 40, comprises osmotically active component(s), but does not contain any pharmaceutical agent. In an embodiment of the present invention, push layer 40 comprises osmopolymer 41. Preferably, the components in push layer 40 comprise an osmoagent 42 (represented by very large circles) and  
25 one or more osmopolymers 41 (represented by "V" symbols).

[000150] Additional, optional excipients within push layer 40, may include binder 43 (represented by down-ward triangles), lubricant 44 (represented by upward semi-circles), antioxidant 45 (represented by diagonal lines) and / or colorant 46 (represented by vertical wavy lines).

30 [000151] As water is imbibed through the semi-permeable wall 20, the osmopolymer(s) within push layer 40 swell and push against drug composition 30 to thereby facilitate release of the drug composition through the exit orifice 60 and thus the pharmaceutical agent from the dosage form.

**[000152]** In an embodiment of the present invention, drug composition 30, as described with reference to Figures 2 and 3 comprises a pharmaceutical agent (for example, topiramate) and solubilizing agent 33 in an admixture with further, optional, selected excipients. The excipients may be one or more  
5 selected from a structural polymer 32, lubricant 34, an osmoagent 35 and / or a binder 36.

**[000153]** In another embodiment of the present invention, push layer 40, as described with reference to Figure 3, comprises osmotically active components, more specifically an osmoagent 42 and an osmopolymer 41, but  
10 does not contain any pharmaceutical agent.

**[000154]** Figure 4 is a view of another embodiment of the present invention, a biconvex round standard tablet as in Figure 1, wherein the tablet includes a further, optional immediate release coating 50 of a pharmaceutical agent, preferably topiramate, covering the dosage form of Figure 1, 2 or 3.

**[000155]** More specifically, dosage form 10 of Figure 4 comprises an overcoat 50 on the outer surface of semi-permeable wall 20 of dosage form 10. Overcoat 50 is a drug composition comprising about 10 µg to about 500 mg of drug 31, preferably, overcoat 50 comprises about 10 µg to about 200 mg of drug 31, more preferably, overcoat 50 comprises about 5 mg to about 100 mg  
20 of drug 31 and from about 5 mg to about 200 mg of a pharmaceutically acceptable carrier selected from the group consisting of alkylcellulose, hydroxyalkylcellulose and hydroxypropylalkylcellulose. The overcoat pharmaceutically acceptable carrier is represented by a polymer or copolymer such as methylcellulose, hydroxyethylcellulose, hydroxybutylcellulose,  
25 hydroxypropylcellulose, hydroxypropylmethylcellulose, hydroxypropylethylcellulose and hydroxypropylbutylcellulose, polyvinyl pyrrolidone/vinyl acetate copolymer, polyvinyl alcohol-polyethylene graft copolymer, and the like. Overcoat 50 provides immediate release of the pharmaceutical agent, as overcoat 50 dissolves in the presence of  
30 gastrointestinal fluid and concurrently therewith delivers drug 31 into the gastrointestinal tract for immediate therapy. Drug 31 in overcoat 50 can be the same or different than the drug 31 in drug composition 30. Preferably drug 31

in overcoat 50 is the same as drug 31 in drug composition 30. More preferably drug 31 is topiramate.

**[000156]** Figure 5 illustrates another, preferred embodiment of the present invention, illustrating an open view of a tri-layer capsule shaped osmotic dosage form. Figure 5 illustrates a capsule shaped tablet embodiment of the present invention comprising a first drug composition 30, a second drug composition 70 and a push layer 40. The capsule shaped core (comprising the first and second drug compositions and the push layer) is enveloped by semi-permeable membrane 20. The dosage form further comprises at least one exit orifice 60 which exposes the first drug composition 30 to the environment of use. The dosage form in Figure 5 further comprises an additional, optional inner membrane 80 that may function as a flow-promoting layer and / or as a smoothing layer and / or contribute to the control of the rate of imbibition of water into the dosage form.

**[000157]** In an embodiment of the present invention, as described in Figure 5, the amount and / or concentration of the drug in the first drug composition 30 is different than the amount and / or concentration of drug in second drug composition 70. In another embodiment of the present invention, the amount and / or concentration of drug in the first drug composition 30 is less than the amount and / or concentration of drug in second drug composition 70. Preferably, the amount and / or concentration of drug in the first drug composition 30 is less than the amount and / or concentration of drug in the second drug composition 70. More preferably, the amounts and / or concentrations of drug in the first and second drug compositions are selected to yield a substantially ascending rate of release of the pharmaceutical agent.

**[000158]** The dosage form illustrated in Figure 5 may further comprise additional drug compositions having varying drug amounts and / or concentrations, to provide alternate release rates and / or patterns and / or to achieve alternate drug plasma concentration profiles that may be preferred.

**[000159]** The drug composition of the present invention comprises two components: (a) a pharmaceutical agent 31, preferably a low solubility and / or low dissolution rate pharmaceutical agent, more preferably topiramate, and (b) a solubilizing agent 33, preferably a surfactant. In an embodiment of the



present invention, the drug composition comprises (a) a pharmaceutical agent 31, preferably a low solubility and / or low dissolution rate pharmaceutical agent, more preferably, topiramate, (b) a solubilizing agent 33, preferably a surfactant and (c) a structural polymer 32. The drug composition may further, optionally contain one or more excipients, as herein described.

**[000160]** In a preferred embodiment of the present invention, the pharmaceutical agent in drug layer 30 is present in a therapeutically effective amount. In another embodiment of the present invention, the total amount of pharmaceutical agent present in the drug composition or compositions of the dosage forms of the present invention, is equal to or greater than the therapeutically effective, recommended or desired daily dosage.

**[000161]** In an embodiment of the present invention, the pharmaceutical agent in drug composition 30 (or wherein the dosage form comprises more than one drug composition, the pharmaceutical agent in the combined drug compositions) is present in an amount equal to or greater than the recommended or desired daily dosage of the pharmaceutical agent to be administered to a patient in need thereof, thereby permitting once-a-day or less frequent dosing.

**[000162]** Wherein the dosage form contains more than one drug composition, as for example in Figure 5 wherein two drug compositions 30 and 70 are present, each drug composition comprises independently selected (a) pharmaceutical agent 31, preferably a low solubility and / or low dissolution rate pharmaceutical agent, more preferably topiramate and (b) solubilizing agent 33, preferably surfactant. Each drug composition may further optionally contain independently selected structural polymer 32 and / or one or more independently selected excipients as hereinafter described.

**[000163]** Wherein two or more drug compositions are present within the dosage forms of the present invention, the daily dosage of the pharmaceutical agent is present in divided amounts. For example, if the dosage of the pharmaceutical agent is 400 mg, and the dosage form comprises two drug compositions (e.g. drug compositions 30 and 70 as exemplified in Figure 5), then the sum of the amount of pharmaceutical agent in the first drug

composition plus the amount of pharmaceutical agent in the second drug composition will total 400 mg or more.

5     **[000164]**     Wherein two drug compositions are present with the dosage forms of the present invention, the ratio of the drug concentration in the second drug composition 70 to the drug concentration in the first drug composition 30, as illustrated in Figure 5, is preferably in the range of from about 1.0 to about 2.5, preferably, about 1.0 to about 2.0, more preferably, about 1.25 and about 1.75.

10     **[000165]**     Pharmaceutical agent 31 is preferably a low solubility and / or low dissolution rate pharmaceutical agent, more preferably, topiramate. Topiramate is in the therapeutic category of anticonvulsants. The solubility of neat topiramate is in the range of about 9.8 mg/ml to 13.0 mg/ml, with solubility in de-ionized water measured to be about 12 mg/ml.

15     **[000166]**     Pharmaceutical agent 31 may be provided in the drug composition in an amount in the range of from about 1 mg to about 750 mg per dosage form. Preferably, the pharmaceutical agent is present in an amount in the range of from about 1 mg to about 250 mg per dosage form, and more preferably, in the range of from about 5 mg to about 250 mg. The amount of pharmaceutical agent within the dosage form will depend upon the required dosing level that must be maintained over the delivery period, i.e., the time between consecutive administrations of the dosage forms. In an embodiment of the present invention, the pharmaceutical agent is present in an amount in the range of from about 5 mg to about 250 mg, more preferably, in an amount in the range of from about 10 mg to about 250 mg per day.

20     **[000167]**     Preferably, pharmaceutical agent 31 is present in the drug composition in micronized form. Preferably, the micronized pharmaceutical agent has a nominal particle size of less than about 200 microns, more preferably less than about 100 microns, most preferably, less than about 50 microns.

30     **[000168]**     Solubilizing agent 33, preferably a pharmaceutically acceptable solubilizing agent, more preferably, a surfactant, is included in the drug composition(s) of the dosage forms of the present invention, as represented by vertical dashes in Figure 2 and Figure 3.

**[000169]** It is well known that solubilizing agents, more particularly surfactants, can be used in liquid drug delivery systems as wetting agents, drug solubilizers, meltable carriers, oily liquid fills in gel capsules for oral administration, parenteral liquids for injection, ophthalmic drops, topical ointments, salves, lotions, and creams, suppositories, and in pulmonary and nasal sprays. By their amphipathic molecular structure comprising opposing polar hydrophilic and non-polar hydrophobic moieties with opposite physical and chemical properties, surfactants are well known to have poor cohesive properties. Accordingly, surfactants have been limited to the above applications because at room temperature, such surfactants are in the physical form of liquids, pastes, or brittle solids, which physical forms and properties are generally unacceptable for use as components in compressed solid tablets sufficiently durable for manufacture and practical use.

**[000170]** As noted, surfactants typically have poor cohesive properties and therefore do not compress as hard, durable tablets. Furthermore, surfactants are in the physical form of liquid, pastes, or waxy solids at standard temperatures and conditions and are inappropriate for tableted oral pharmaceutical dosage forms. However, it has been unexpectedly found that surfactants may be used in accordance with the drug compositions and dosage forms of the present invention to enhance the solubility of the pharmaceutical agent and potentially, the bioavailability of the pharmaceutical agent.

**[000171]** A class of solubilizing agents which may be used in the drug compositions and / or dosage forms of the present invention include, for example, a surfactant of POLYOXYL 40 stearate (also known as MYRJ 52) and POLYOXYL 50 stearate (also known as MYRJ 53). Preferably, the solubilizing agent is a drug solubilizing surfactant selected from the group polyethylene glycol (PEG) 3350; PEG 8K; KOLLIDON K90; PLURONIC F 68, F87, F127, F108; MYRJ 52S; and PVP K2939. Preferably, the solubilizing agent is the surfactant PLURONIC F127.

**[000172]** Another class of surfactant which may be used in the drug compositions and / or dosage forms of the present invention is a group of copolymers of ethylene oxide and propylene oxide conforming to the general formula  $\text{OH}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})$ , also known as poloxamers or by their

tradenames PLURONICS and LUTROLS. In this class of surfactants, the hydrophilic ethylene oxide ends of the surfactant molecule and the hydrophobic midblock of propylene oxide of the surfactant molecule serve to dissolve and suspend the drug in the pumpable hydrogel.

5     **[000173]**     Other surfactants that are solids at room temperature and which may be used in the drug compositions and / or dosage forms of the present invention include members selected from the group essentially consisting of sorbitan monopalmitate, sorbitan monostearate, glycerol monostearate, polyoxyethylene stearate (self emulsifying), polyoxyethylene 40 sorbitol lanolin  
10     derivative, polyoxyethylene 75 sorbitol lanolin derivative, polyoxyethylene 6 sorbitol beeswax derivative, polyoxyethylene 20 sorbitol beeswax derivative, polyoxyethylene 20 sorbitol lanolin derivative, polyoxyethylene 50 sorbitol lanolin derivative, polyoxyethylene 23 lauryl ether, polyoxyethylene 23 lauryl ether with butylated hydroxyanisole and citric acid added as preservatives,  
15     polyoxyethylene 2 cetyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 10 cetyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 20 cetyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 2 stearyl ether with butylated hydroxyanisole and citric acid  
20     added as preservatives, polyoxyethylene 10 stearyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 20 stearyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 21 stearyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 20 oleyl ether with  
25     butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 40 stearate, polyoxyethylene 50 stearate, polyoxyethylene 100 stearate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, polyoxyethylene 4 sorbitan monostearate, polyoxyethylene 20 sorbitan tristearate, and the like. "Handbook of Pharmaceutical Excipients", 2<sup>nd</sup> Ed.  
30     Ainley Wade and Paul J. Weller Editors, 1994

**[000174]**     An especially preferred family of surfactants are a:b:a triblock copolymers of ethylene oxide:propylene oxide:ethylene oxide. The "a" and "b" represent the average number of monomer units for each block of the polymer

chain. These surfactants are commercially available from BASF Corporation of Mount Olive, New Jersey, in a variety of different molecular weights and with different values of "a" and "b" blocks. For example, LUTROL® F127 has a molecular weight range of 9,840 to 14,600 and where "a" is approximately 101 and "b" is approximately 56, LUTROL F87 represents a molecular weight of 6,840 to 8,830 where "a" is 64 and "b" is 37, LUTROL F108 represents an average molecular weight of 12,700 to 17,400 where "a" is 141 and "b" is 44, and LUTROL F68 represents an average molecular weight of 7,680 to 9,510 where "a" has a value of about 80 and "b" has a value of about 27. A resource of surfactants including solid surfactants and their properties is available in McCutcheon's Detergents and Emulsifiers, International Edition 1979 and McCutcheon's Detergents and Emulsifiers, North American Edition 1979. Other sources of information on properties of solid surfactants include BASF Technical Bulletin PLURONIC & TETRONIC Surfactants 1999 and General Characteristics of Surfactants from ICI Americas Bulletin 0-1 10/80 5M.

**[000175]** One of the characteristics of surfactants tabulated in these references is the HLB value, or hydrophilic lipophilic balance value. This value represents the relative hydrophilicity and relative hydrophobicity of a surfactant molecule. Generally, the higher the HLB value, the greater the hydrophilicity of the surfactant while the lower the HLB value, the greater the hydrophobicity. For the LUTROL molecules, for example, the ethylene oxide fraction represents the hydrophilic moiety and the propylene oxide fraction represents the hydrophobic fraction. The HLB values of LUTROL F127, F87, F108, and F68 are respectively 22.0, 24.0, 27.0, and 29.0.

**[000176]** Other particularly preferred surfactants include sugar ester surfactants, which are sugar esters of fatty acids. Such sugar ester surfactants include sugar fatty acid monoesters, sugar fatty acid diesters, triesters, tetraesters, or mixtures thereof, although mono- and di-esters are most preferred. Preferably, the sugar fatty acid monoester comprises a fatty acid having from 6 to 24 carbon atoms, which may be linear or branched, or saturated or unsaturated C<sub>6</sub> to C<sub>24</sub> fatty acids. The C<sub>6</sub> to C<sub>24</sub> fatty acids include C<sub>6</sub>, C<sub>7</sub>, C<sub>8</sub>, C<sub>9</sub>, C<sub>10</sub>, C<sub>11</sub>, C<sub>12</sub>, C<sub>13</sub>, C<sub>14</sub>, C<sub>15</sub>, C<sub>16</sub>, C<sub>17</sub>, C<sub>18</sub>, C<sub>19</sub>, C<sub>20</sub>, C<sub>21</sub>, C<sub>22</sub>, C<sub>23</sub>, and C<sub>24</sub> in any subrange or combination. These esters are preferably chosen



from stearates, behenates, cocoates, arachidonates, palmitates, myristates, laurates, carprates, oleates, laurates and their mixtures.

**[000177]** Preferably, the sugar fatty acid monoester comprises at least one saccharide unit, such as sucrose, maltose, glucose, fructose, mannose, galactose, arabinose, xylose, lactose, sorbitol, trehalose or methylglucose. Disaccharide esters such as sucrose esters are most preferable, and include sucrose cocoate, sucrose monooctanoate, sucrose monodecanoate, sucrose mono- or dilaurate, sucrose monomyristate, sucrose mono- or dipalmitate, sucrose mono- and distearate, sucrose mono-, di- or trioleate, sucrose mono- or dilinoleate, sucrose polyesters, such as sucrose pentaoleate, hexaoleate, heptaoleate or octooleate, and mixed esters, such as sucrose palmitate/stearate.

**[000178]** Particularly preferred examples of such sugar ester surfactants include those sold by the company Croda Inc of Parsippany, NJ under the names CRODESTA F10, F50, F160, and F110 denoting various mono-, di- and mono/di ester mixtures comprising sucrose stearates, manufactured using a method that controls the degree of esterification, such as described in U.S. Patent No. 3,480,616. These preferred sugar ester surfactants provide the added benefit of tableting ease and nonsmearing granulation. The sugar ester surfactants may also provide enhanced compatibility with sugar based therapeutic agents, exemplified by topiramate.

**[000179]** Sugar surfactants sold by the company Mitsubishi under the name RYOTO SUGAR ESTERS, for example under the reference B370 corresponding to sucrose behenate formed of 20% monoester and 80% di-, tri- and polyester may also be used. Use may also be made of the sucrose mono- and dipalmitate/stearate sold by the company Goldschmidt under the name "TEGOSOFT PSE". Use may also be made of a mixture of these various products. The sugar ester can also be present in admixture with another compound not derived from sugar; and a preferred example includes the mixture of sorbitan stearate and of sucrose cocoate sold under the name "ARLATONE 2121" by the company ICI. Other sugar esters include, for example, glucose trioleate, galactose di-, tri-, tetra- or pentaoleate, arabinose di-, tri- or tetralinoleate or xylose di-, tri- or tetralinoleate, or mixtures thereof.

Other sugar esters of fatty acids include esters of methylglucose include the distearate of methylglucose and of polyglycerol-3 sold by the company Goldschmidt under the name of TEGOCARE 450. Glucose or maltose monoesters can also be included, such as methyl O-hexadecanoyl-6-D-glucoside and O-hexadecanoyl-6-D-maltose. Certain other sugar ester surfactants include oxyethylenated esters of fatty acid and of sugar include oxyethylenated derivatives such as PEG-20 methylglucose sesquistearate, sold under the name "GLUCAMATE SSE20", by the company Amerchol.

**[000180]** Solubilizing agent 33 can be one surfactant or a blend of surfactants. The surfactants are selected such that they have values that promote the dissolution and solubility of the drug. A high HLB surfactant can be blended with a surfactant of low HLB to achieve a net HLB value that is between them, if a particular drug requires the intermediate HLB value. Surfactant 33 is selected depending upon the drug being delivered; such that the appropriate HLB grade is utilized.

**[000181]** Preferably, the solubilizing agent is selected from the group consisting of MYRJ 52, MYRJ 53, MYRJ 59FL, KOLLIDON 12PF, KOLLIDON 17PF, KOLLIDON 25/30, KOLLIDON K90, LUTROL F68, LUTROL F87, LUTROL F127, LUTROL F108; PVP K2932, polyethylene glycol (PEG) 3350; PEG 8K; sorbitan monopalmitate, sorbitan monostearate, glycerol monostearate, polyoxyethylene stearate, sucrose cocoate, polyoxyethylene 40 sorbitol lanolin derivative, polyoxyethylene 75 sorbitol lanolin derivative, polyoxyethylene 6 sorbitol beeswax derivative, polyoxyethylene 20 sorbitol beeswax derivative, polyoxyethylene 20 sorbitol lanolin derivative, polyoxyethylene 50 sorbitol lanolin derivative, polyoxyethylene 23 lauryl ether, polyoxyethylene 23 lauryl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 2 cetyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 2 stearyl ether, polyoxyethylene 21 stearyl ether, polyoxyethylene 100 stearyl ether, polyoxyethylene 10 cetyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 20 cetyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 2 stearyl ether with butylated hydroxyanisole and citric acid added as

preservatives, polyoxyethylene 10 stearyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 20 stearyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 21 stearyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 20 oleyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 40 stearate, polyoxyethylene 50 stearate, polyoxyethylene 100 stearate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, polyoxyethylene 4 sorbitan monostearate, polyoxyethylene 20 sorbitan tristearate, and mixtures thereof.

**[000182]** More preferably, the solubilizing agent is a surfactant selected from the group consisting of LUTROL F68, LUTROL F87, LUTROL 108, LUTROL F127, MYRJ 52, MYRJ 53; most preferably, the solubilizing agent is the surfactant LUTROL F127.

**[000183]** In a preferred embodiment of the present invention, the surfactant is not a sugar ester.

**[000184]** Preferably, in the drug compositions and / or dosage forms of the present invention, the pharmaceutical agent is matched with a suitable, aforementioned solubilizing agent, preferably, a solid surfactant or mixture of surfactants.

**[000185]** A suitable surfactant may be selected by preparing aqueous solutions of selected surfactants spanning a range of HLB values and a range of concentrations. Then, the pharmaceutical agent is added in excess to the surfactant solutions and the saturated solubility of the pharmaceutical agent (at equilibrium) is measured by an appropriate analytical method such as ultraviolet spectroscopy, chromatographic methods, or gravimetric analysis. The solubility values are then plotted as a function of HLB and as a function of surfactant concentration. The solubilizing agent (preferably surfactant) can then be selected by evaluating the maximal point of solubility generated in the plots at the different concentrations.

**[000186]** Preferably, wherein the pharmaceutical agent is topiramate, the solubilizing agent is a surfactant, preferably, the surfactant is PLURONIC F127 or its corresponding pharmaceutically acceptable grade LUTROL F127.

**[000187]** Preferably, the solubilizing agent, preferably surfactant, is present in the drug composition in micronized form. Preferably, the micronized solubilizing agent, preferably surfactant, has a nominal particle size of less than about 200 microns, more preferably, less than about 100 microns, most preferably, less than about 50 microns.

**[000188]** To achieve a substantially zero order release rate profile, the ratio of solubilizing agent, preferably surfactant, to pharmaceutical agent is preferably, in the range of from about 1.3 to about 2.7, more preferably, in the range of from about 1.5 to about 2.5, more preferably still, in the range of from about 1.8 to about 2.2.

**[000189]** To achieve a substantially ascending release rate profile, the ratio of solubilizing agent, preferably surfactant, to pharmaceutical agent is preferably, in the range of from about 0.1:1 to about 3:1, more preferably, in the range of from about 0.25:1 to about 2.5:1, more preferably, in the range of from about 0.5:1 to about 2:1, more preferably still, in the range of from about 1:1 to about 2:1, more preferably still, in the range of from about 1.5:1 to about 2:1.

**[000190]** The present invention may provide a potentially beneficial increased bioavailability to the low solubility and / or low dissolution rate drug by increasing its solubility and wetted surface for greater bioadhesion to the gastrointestinal tract mucosa. The wetting properties of the solubilizing agent (preferably surfactant) may also have the effect of preventing the released drug from agglomerating upon release into the environment of use, thereby leading to a more complete spreading of the dispensed drug composition onto the absorbable surfaces of the gastrointestinal tract. The resulting increased surface area may provide more absorption surface area to increase the rate and extent of drug absorbed and thus increase the therapeutic response.

**[000191]** The solubilizing agent (preferably surfactant) may further impart adhesive character to the dispensed drug composition, which adhesive character may prolong the contact time between the drug composition and the absorbable mucosal tissue of the gastrointestinal tract, thereby providing more time for the drug to be spread and be absorbed once delivered.

**[000192]** In yet another potential beneficial effect, the solubilizing agent (preferably surfactant) may additionally increase the permeability of mucosal membranes to the drug molecule which permeability enhancement may lead to enhanced bioavailability of the drug and enhanced therapeutic response.

5 **[000193]** When drug 31 is present in low dosage amounts, less than about 20% by weight of the drug composition 30, the present invention may provide a beneficial increased bioavailability of the low solubility and / or low dissolution rate drug, by increasing its solubility and wetted surface for greater  
10 bioadhesion to the gastrointestinal tract mucosa and enhanced permeability of the mucosal surfaces. The increased drug solubility, the increased surface contact area on the mucosal tissue, the increased contact time to the mucosal tissue, and permeability enhancement of the mucosal tissue to the drug molecule may individually or compositely contribute to the overall therapeutic enhancement of the drug by the present invention.

15 **[000194]** Structural polymer 32 comprises any component, for example a hydrophilic polymer, which provides cohesiveness to the blend so durable tablets can be made. The structural polymer may also form a hydrogel for viscosity control during the operation of the delivery system. The structural polymer further suspends the drug particles to promote partial or complete  
20 solubilization of the drug within the dosage form prior to delivery from the dosage form.

**[000195]** The molecular weight of the structural polymer 32 may be chosen to impart desired properties to the dosage form, and more particularly to the drug compositions within the dosage form. High molecular weight polymers  
25 are used to produce a slow hydration rate and slow delivery of drug, whereas low molecular weight polymers produce a faster hydration rate and faster release of drug. A blend of high and low molecular weight structural polymers produces an intermediate delivery rate.

**[000196]** If the drug composition of the present invention is used in an  
30 erodible matrix dosage form, the molecular weight of the structural polymer is selected to modify the erosion rate of the system. High molecular weight polymers are used to produce slow erosion rate and slow delivery of drug, whereas low molecular weight polymers produce a faster erosion rate and



faster release of drug. A blend of high and low molecular weight structural polymers produces an intermediate delivery rate.

5     **[000197]**     If the drug composition of the present invention is used in a non-erodible porous matrix dosage form, the molecular weight of the structural polymer is selected to provide a viscous hydrogel within the pores of the matrix.

The viscosity of the hydrogel serves to suspend drug particles to promote partial or complete solubilization of the drug in the presence of the surfactant prior to delivery from the pores of the dosage form.

10     **[000198]**     Structural polymer 32 is a hydrophilic polymer particle in the drug composition that contributes to the controlled delivery of active agent. Representative examples of suitable structural polymers include, but are not limited to, poly(alkylene oxide) of 100,000 to 750,000 number-average molecular weight, including poly(ethylene oxide), poly(methylene oxide), poly(butylene oxide) and poly(hexylene oxide); and a  
15     poly(carboxymethylcellulose) of 40,000 to 1,000,000 400,000 number-average molecular weight, represented by poly(alkali carboxymethylcellulose), poly(sodium carboxymethylcellulose), poly(potassium carboxymethylcellulose) poly(calcium carboxymethylcellulose), and poly(lithium  
20     carboxymethylcellulose). The drug composition may alternatively comprise a hydroxypropylalkylcellulose of 9,200 to 125,000 number-average molecular weight for enhancing the delivery properties of the dosage form such as hydroxypropylethylcellulose, hydroxypropylmethylcellulose, hydroxypropylbutylcellulose, hydroxypropylpentylcellulose, and the like; and / or  
25     a poly(vinylpyrrolidone) of 7,000 to 75,000 number-average molecular weight for enhancing the flow properties of the dosage form. Preferred structural polymers are the poly(ethylene oxide) polymers of 100,000 - 300,000 number average molecular weight. Structural polymers that erode in the gastric environment, i.e., bioerodible structural polymers, are especially preferred.

30     **[000199]**     Other structural polymers that may be incorporated into drug composition 30 include carbohydrates that exhibit sufficient osmotic activity to be used alone or with other osmoagents. Such carbohydrates comprise monosaccharides, disaccharides and polysaccharides. Representative examples include, but are not limited to, maltodextrins (i.e., glucose polymers

produced by the hydrolysis of grain starch such as rice or corn starch) and the sugars comprising lactose, glucose, raffinose, sucrose, mannitol, sorbitol, zylitol and the like. Preferred maltodextrins are those having a dextrose equivalence (DE) of about 20 or less, preferably maltodextrins with a DE  
5 ranging from about 4 to about 20, and more preferably from about 9 to about 20. Maltodextrins having a DE of about 9-12 and molecular weight of about 1,600 to 2,500 are preferred.

**[000200]** The carbohydrates described above, preferably the maltodextrins, may be used in the drug composition 30 without the addition of  
10 an osmoagent, to yield the desired release of pharmaceutical agent from the dosage form, while providing a therapeutic effect over a prolonged period of time and up to 24 hours with once-a-day dosing.

**[000201]** Preferably, the structural polymer is selected from the group consisting of poly(ethylene oxide), poly(methylene oxide), poly(butylene oxide)  
15 and poly(hexylene oxide); poly(carboxymethylcellulose), poly(alkali carboxymethylcellulose), poly(sodium carboxymethylcellulose), poly(potassium carboxymethylcellulose) poly(calcium carboxymethylcellulose), poly(lithium carboxymethylcellulose), hydroxypropylcellulose, hydroxypropylethylcellulose, hydroxypropylmethylcellulose, hydroxypropylbutylcellulose,  
20 hydroxypropylpentylcellulose, poly(vinylpyrrolidone), a bioerodible structural polymer, maltodextrin, polyvinyl pyrrolidone, a polyvinylpyrrolidone vinyl acetate copolymer, lactose, glucose, raffinose, sucrose, mannitol, sorbitol, zylitol and mixtures thereof.

**[000202]** More preferably, the structural polymer is selected from the group  
25 consisting of MALTRIN M100, POLYOX N10 and POLYOX N80, most preferably, the structural polymer is POLYOX N80.

**[000203]** It has been further found that, when present, the structural polymer and solubilizing agent (preferably surfactant) are preferably present in the drug composition in a certain amounts. Preferably, the structural polymer  
30 should be present in an amount less than or equal to about 90% by weight of the drug composition and the surfactant should be present in amount between 0 and about 50% by weight of the drug composition. Preferably, for high dosages, the structural polymer should be present in an amount less than or

equal to about 30% by weight of the drug composition, more preferably in an amount less than about 20% by weight of the drug composition; and the surfactant should be present in amount greater than or equal to about 15% by weight of the drug composition, more preferably, in an amount greater than or equal to about 25% by weight of the drug composition, more preferably still, in an amount greater than or equal to about 35% by weight of the drug composition, most preferably, in an amount greater than or equal to about 40% by weight of the drug composition.

**[000204]** For high dosages, a preferred range of concentration of structural polymer within the drug composition of osmotic delivery systems is from about 5% to about 50% weight percent of polyoxyethylene 200,000 molecular weight (POLYOX N80), with an especially preferred range of from 0 to about 20% by weight of the drug composition.

**[000205]** For low dosages, a preferred range of concentration of structural polymer within the drug composition of osmotic delivery systems is from about 50% to about 90% weight percent of polyoxyethylene 200,000 molecular weight (POLYOX N80), with an especially preferred range of from 75% to about 90% by weight of the drug composition.

**[000206]** Lubricant 34 may optionally be included in the drug composition as represented by a horizontal wavy line in Figure 2 and Figure 3. Lubricant 34 is used during tablet manufacture to prevent adherence to die walls or punch faces. Typical lubricants include, but are not limited to, magnesium stearate, sodium stearate, stearic acid, calcium stearate, magnesium oleate, oleic acid, potassium oleate, caprylic acid, sodium stearyl fumarate, and magnesium palmitate or blends of such lubricants. The amount of lubricant present in the drug composition is preferably, in the range of from about 0.01 to about 20 mg.

**[000207]** Binder 36, preferably a therapeutically acceptable vinyl polymer binder, may also be optionally included in the drug composition as represented by small circles in Figure 2 and Figure 3. Representative binders include, but are not limited to vinyl polymer binder, acacia, starch and gelatin. Wherein the binder is a vinyl polymer, the vinyl polymer comprises a 5,000 to 350,000 average molecular weight, represented by a member selected from the group consisting of poly-n-vinylamide, poly-n-vinylacetamide, poly(vinyl pyrrolidone),

also known as poly-n-vinylpyrrolidone, poly-n-vinylcaprolactone, poly-n-vinyl-5-methyl-2-pyrrolidone, and poly-n-vinylpyrrolidone copolymers with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laurate, and vinyl stearate. Representative  
5 other binders suitable for formulation in the drug composition include, but are not limited to acacia, starch and gelatin. The binder present within the drug composition is preferably, in an amount in the range of from about 0.01 to about 25 mg.

**[000208]** Disintegrants may also be optionally included in the drug  
10 composition. Disintegrants may be selected from starches, clays, celluloses, algin and gums and crosslinked starches, celluloses and polymers. Representative disintegrants include, but are not limited to, corn starch, potato starch, croscarmellose, crospovidone, sodium starch glycolate, VEEGUM HV, methylcellulose, agar, bentonite, carboxymethylcellulose, alginic acid, guar  
15 gum, low-substituted hydroxypropyl cellulose, microcrystalline cellulose, and the like.

**[000209]** In an embodiment of the present invention, at least one drug composition within a dosage form comprises a pharmaceutical agent and a solubilizing agent. Preferably, the pharmaceutical agent is topiramate and the  
20 solubilizing agent is a surfactant, more preferably, the solubilizing agent is the surfactant PLURONIC F127 or its corresponding pharmaceutically acceptable grade LUTROL F127.

**[000210]** It has further been found that the surfactant appears to be capable of operating as both a structural polymer as well as a surfactant, and  
25 as such it may be utilized as the sole excipient in the drug composition.

**[000211]** , Wherein a drug composition comprises pharmaceutical agent 31, solubilizing agent 33, preferably a surfactant, and structural polymer 32, the amount of structural polymer 32 and surfactant 33 formulated within said drug composition must be appropriately selected and controlled.

**[000212]** One skilled in the art will recognize that the amounts of solubilizing agent and structural polymer are selected to optimize the characteristics of the drug layer composition. The amounts are selected such that the dosage form maintains structural integrity before administration and

upon administration, the drug layer composition hydrates and is capable of being pushed out of the dosage form providing a desired release pattern.

**[000213]** In an embodiment of the present invention is a drug composition, wherein the pharmaceutical agent is topiramate and wherein the topiramate is present in amount in the range of about 10 mg to about 200 mg. In further embodiments of the present invention are drug compositions wherein topiramate is present in 10 mg, 20 mg, 40 mg, 45 mg, 80 mg, 90 mg, 120 mg, 135 mg, 160 mg, 180 mg and 200 mg amount.

**[000214]** In an embodiment of the present invention is a dosage form comprising one or more drug compositions, preferably one to two drug compositions, wherein the total amount of topiramate present within the dosage form (i.e. the total amount present within the drug compositions) is in an amount in the range of about 10 mg to about 200 mg. In further embodiments of the present invention are dosage forms comprising one or two drug compositions wherein the total amount of topiramate present is 10 mg, 20 mg, 40 mg, 45 mg, 80 mg, 90 mg, 120 mg, 135 mg, 160 mg, 180 mg or 200 mg amount.

**[000215]** In an embodiment of the present invention is a dosage form comprising a first drug composition comprising pharmaceutical agent, preferably a low solubility and / or low dissolution rate solubilizing agent, more preferably topiramate and a solubilizing agent, preferably surfactant; and a second drug composition comprising pharmaceutical agent, preferably a low solubility and / or low dissolution rate solubilizing agent, more preferably topiramate and a solubilizing agent, preferably surfactant.

**[000216]** In another embodiment of the present invention is a dosage form comprising (a) a core comprising a first drug composition comprising pharmaceutical agent, preferably a low solubility and / or low dissolution rate solubilizing agent, more preferably topiramate and a solubilizing agent, preferably surfactant; and a push layer comprising an osmopolymer; (b) a semi-permeable wall surrounding said core and (c) an exit orifice through the semi-permeable wall for releasing the pharmaceutical agent from the dosage form over a prolonged period of time.



**[000217]** In yet another embodiment of the present invention is a dosage form comprising (a) a core comprising a first drug composition comprising pharmaceutical agent, preferably a low solubility and / or low dissolution rate solubilizing agent, more preferably topiramate and a solubilizing agent, preferably surfactant; a second drug composition comprising pharmaceutical agent, preferably a low solubility and / or low dissolution rate solubilizing agent, more preferably topiramate and a solubilizing agent, preferably surfactant; and a push layer comprising an osmopolymer; (b) a semi-permeable wall surrounding said core and (c) an exit orifice through the semi-permeable wall for releasing the pharmaceutical agent from the dosage form over a prolonged period of time.

**[000218]** One skilled in the art will recognize will that wherein the dosage forms of the present invention comprise a first drug composition comprising a pharmaceutical agent and a solubilizing agent; and a second drug composition comprising a pharmaceutical agent and a solubilizing agent; then the pharmaceutical agent in the first and second drug compositions may be the same or different and the solubilizing agent on the first and second drug compositions may be the same or different. One skilled in the art will further recognize that additional, optional components within the first and second drug compositions, for example structural polymer, binder, lubricant, and the like, when present in both the first and second drug compositions may similarly be the same or different.

**[000219]** The formulations and processes for the manufacture of the push layer 40, the semi-permeable wall 20 and the exit orifice(s) 60 are well known in the art. The components and processes for the manufacture of the push layer, semi-permeable wall and exit orifice(s) is also briefly described below.

**[000220]** Push layer 40 comprises a displacement composition in contacting, layered arrangement with drug composition 30 as illustrated in Figure 3. Wherein more than one drug composition is present in the dosage form (as in Figure 5), the push layer 40 is preferably in contacting, layered arrangement with only one of the drug compositions.

[000221] In an embodiment of the present invention push layer 40 comprises an osmopolymer. In another embodiment of the present invention, push layer 40 comprises an osmopolymer and an osmoagent.

[000222] Push layer 40 comprises osmopolymer 41 that imbibes water and swells to push the drug composition of the drug layer(s) through the exit orifice of the dosage form. The osmopolymers are swellable, hydrophilic polymers that interact with water and swell or expand to a high degree, typically exhibiting a 2-50 fold volume increase. The osmopolymer can be non-crosslinked or crosslinked. Preferably, push layer 40 comprises from about 20 to about 375 mg of osmopolymer 41, represented by "V" symbols in Figure 3.

[000223] Wherein osmopolymers are present in both a drug composition and the push layer, the osmopolymer 41 in the push layer 40 possesses a higher molecular weight than the osmopolymer in drug composition. For example, such a situation may be found wherein the structural polymer in the drug composition is an osmopolymer.

[000224] Representatives of osmopolymers (i.e. fluid-imbibing displacement polymers) comprise members selected from poly(alkylene oxide) of 1 million to 15 million number-average molecular weight, as represented by poly(ethylene oxide), and poly(alkali carboxymethylcellulose) of 500,000 to 3,500,000 number-average molecular weight, wherein the alkali is sodium, potassium or lithium. Examples of alternate osmopolymers comprise polymers that form hydrogels, such as CARBOPOL<sup>®</sup> acidic carboxypolymer, a polymer of acrylic cross-linked with a polyallyl sucrose, also known as carboxypolymethylene, and carboxyvinyl polymer having a molecular weight of 250,000 to 4,000,000; CYANAMER<sup>®</sup> polyacrylamides; cross-linked water swellable indenemaleic anhydride polymers; GOOD-RITE<sup>®</sup> polyacrylic acid having a molecular weight of 80,000 to 200,000; AQUA-KEEPS<sup>®</sup> acrylate polymer polysaccharides composed of condensed glucose units, such as diester cross-linked polygluran; and the like. Representative polymers that form hydrogels are known to the prior art in U.S. Patent No. 3,865,108, issued to Hartop; U.S. Patent No. 4,002,173, issued to Manning; U.S. Patent No. 4,207,893, issued to Michaels; and in Handbook of Common Polymers, Scott and Roff, Chemical Rubber Co., Cleveland, OH.

**[000225]** Push layer 40 further, optionally, comprises an osmotically effective compound, osmoagent 42, represented by large circles in Figure 3. Preferably, the osmoagent 42 comprises up to about 40% by weight of the push layer, more preferably, from about 5% to about 30% by weight of the push layer, more preferably still, from about 10% to about 30% by weight of the push layer. Osmotically effective compounds are known also as osmoagents and / or as osmotically effective solutes. Preferably, push layer 40 comprises an osmoagent.

**[000226]** Osmoagents 42, which may be found in the drug composition and / or the push layer in the dosage forms of the present invention are those that exhibit an osmotic activity gradient across the wall 20. Suitable osmoagents include, but are not limited to, sodium chloride, potassium chloride, lithium chloride, magnesium sulfate, magnesium chloride, potassium sulfate, sodium sulfate, lithium sulfate, potassium acid phosphate, mannitol, urea, inositol, magnesium succinate, tartaric acid, raffinose, sucrose, glucose, lactose, sorbitol, inorganic salts, organic salts, carbohydrates, and the like.

**[000227]** Push layer 40 may further optionally comprises a pharmaceutically acceptable binder 43, such as a vinyl polymer, represented by triangles in Figure 3. The vinyl polymer comprises a 5,000 to 350,000 viscosity-average molecular weight, represented by a member selected from the group consisting of poly-n-vinylamide, poly-n-vinylacetamide, poly(vinyl pyrrolidone), also known as poly-n-vinylpyrrolidone, poly-n-vinylcaprolactone, poly-n-vinyl-5-methyl-2-pyrrolidone, and poly-n-vinylpyrrolidone copolymers with a member selected from the group consisting of vinyl acetate, vinyl alcohol, vinyl chloride, vinyl fluoride, vinyl butyrate, vinyl laurate, and vinyl stearate. Push layer 40 preferably contains from about 0.01 to about 25 mg of vinyl polymer.

**[000228]** Push layer 40 may further optionally comprise from 0 to about 5 mg of a nontoxic colorant or dye 46, identified by vertical wavy lines in Figure 3. Suitable examples of colorant or dye 46 include Food and Drug Administration Colorants (FD&C), such as FD&C No. 1 blue dye, FD&C No. 4 red dye, red ferric oxide, yellow ferric oxide, titanium dioxide, carbon black, indigo, and the like.

**[000229]** Push layer 40 may further optionally comprise lubricant 44, identified by half circles in Figure 3. Suitable examples include, but are not limited to, a member selected from the group consisting of sodium stearate, potassium stearate, magnesium stearate, stearic acid, calcium stearate, sodium oleate, calcium palmitate, sodium laurate, sodium ricinoleate and potassium linoleate, and blends of such lubricants. The amount of lubricant included in the push layer 40 is preferably in the range of from about 0.01 to about 10 mg.

**[000230]** Push layer 40 may further optionally comprise an antioxidant 45, represented by slanted dashes in Figure 3, wherein the antioxidant is present to inhibit the oxidation of ingredients within the push layer. Push layer 40 comprises from 0.0 to about 5 mg of an antioxidant. Representative antioxidants include, but are not limited to, ascorbic acid, ascorbyl palmitate, butylated hydroxyanisole, a mixture of 2 and 3 tertiary-butyl-4-hydroxyanisole, butylated hydroxytoluene, sodium isoascorbate, dihydroguaric acid, potassium sorbate, sodium bisulfate, sodium metabisulfate, sorbic acid, potassium ascorbate, vitamin E, 4-chloro-2,6-ditertiary butylphenol, alpha-tocopherol, and propylgallate.

**[000231]** Semi-permeable wall 20, sometimes also referred to as a membrane, is formed to be permeable to the passage of external water. Semi-permeable wall 20 is also substantially impermeable to the passage of the components of the drug composition and push layer, such as drug, solubilizing agent, structural polymer, osmagent, osmopolymer and the like. As such, wall 20 is semi-permeable. The selectively semi-permeable compositions used for forming the semi-permeable wall 20 are essentially non-erodible and are substantially insoluble in biological fluids during the life of the dosage form.

**[000232]** Representative polymers suitable for forming semi-permeable wall 20 comprise semi-permeable homopolymers, semi-permeable copolymers, and the like. Such materials include, but are not limited to, cellulose esters, cellulose ethers and cellulose ester-ethers. The cellulosic polymers have a degree of substitution (DS) of their anhydroglucose unit of from greater than 0 up to 3, inclusive. Degree of substitution (DS) means the average number of hydroxyl groups originally present on the anhydroglucose

unit that are replaced by a substituting group or converted into another group. The anhydroglucose unit can be partially or completely substituted with groups such as acyl, alkanoyl, alkenoyl, aroyl, alkyl, alkoxy, halogen, carboalkyl, alkylcarbamate, alkylcarbonate, alkylsulfonate, alkylsulfamate, semi-permeable  
5 polymer forming groups, and the like, wherein the organic moieties contain from one to twelve carbon atoms, and preferably from one to eight carbon atoms.

**[000233]** Semi-permeable wall 20 may further compromise a semi-permeable polymer selected from the group consisting of cellulose acylate,  
10 cellulose diacylate, cellulose triacylate, cellulose acetate, cellulose diacetate, cellulose triacetate, mono-, di- and tri-cellulose alkanylates, mono-, di-, and tri-alkenylates, mono-, di-, and tri-aroylates, and the like. Exemplary polymers include cellulose acetate having a DS in the range of about 1.8 to about 2.3 and an acetyl content in the range of about 32 to about 39.9%; cellulose  
15 diacetate having a DS in the range of about 1 to about 2 and an acetyl content in the range of about 21 to about 35%; cellulose triacetate having a DS in the range of about 2 to about 3 and an acetyl content in the range of about 34 to about 44.8%; and the like. Preferred cellulosic polymers include cellulose propionate having a DS of about 1.8 and a propionyl content of about 38.5%;  
20 cellulose acetate propionate having an acetyl content in the range of about 1.5 to about 7% and an acetyl content in the range of about 39% to about 42%; cellulose acetate propionate having an acetyl content in the range of about 2.5% to about 3%, an average propionyl content in the range of about 39.2% to about 45%, and a hydroxyl content in the range of about 2.8% to about 5.4%;  
25 cellulose acetate butyrate having a DS of about 1.8, an acetyl content in the range of about 13% to about 15%, and a butyryl content in the range of about 34% to about 39%; cellulose acetate butyrate having an acetyl content in the range of about 2% to about 29%, a butyryl content in the range of about 17% to about 53%, and a hydroxyl content in the range of about 0.5% to about  
30 4.7%; cellulose triacylates having a DS in the range of about 2.6 to about 3, such as cellulose trivalerate, cellulose trilamate, cellulose tripalmitate, cellulose trioctanoate and cellulose tripropionate; cellulose diesters having a DS in the range of about 2.2 to about 2.6, such as cellulose disuccinate, cellulose



dipalmitate, cellulose dioctanoate, cellulose dicaprylate, and the like; and mixed cellulose esters, such as cellulose acetate valerate, cellulose acetate succinate, cellulose propionate succinate, cellulose acetate octanoate, cellulose valerate palmitate, cellulose acetate heptanoate, and the like. Semi-permeable polymers are known in U.S. Patent No. 4,077,407, and they can be synthesized by procedures described in Encyclopedia of Polymer Science and Technology, Vol. 3, pp. 325-354 (1964), Interscience Publishers Inc., New York, NY.

**[000234]** Additional semi-permeable polymers that may be used for forming semi-permeable wall 20 comprise cellulose acetaldehyde dimethyl acetate; cellulose acetate ethylcarbamate; cellulose acetate methyl carbamate; cellulose dimethylaminoacetate; semi-permeable polyamide; semi-permeable polyurethanes; semi-permeable sulfonated polystyrenes; cross-linked selectively semi-permeable polymers formed by the coprecipitation of an anion and a cation, as disclosed in U.S. Patents Nos. 3,173,876; 3,276,586; 3,541,005; 3,541,006 and 3,546,142; semi-permeable polymers, as disclosed by Loeb, et al. in U.S. Patent No. 3,133,132; semi-permeable polystyrene derivatives; semi-permeable poly(sodium styrenesulfonate); semi-permeable poly(vinylbenzyltrimethylammonium chloride); and semi-permeable polymers exhibiting a fluid permeability of  $10^{-5}$  to  $10^{-2}$  (cc. mil/cm hr.atm), expressed as per atmosphere of hydrostatic or osmotic pressure differences across a semi-permeable wall. The polymers are known to the art in U.S. Patents Nos. 3,845,770; 3,916,899 and 4,160,020; and in Handbook of Common Polymers, Scott and Roff (1971) CRC Press, Cleveland, OH. Wall 20 can optionally be formed as two or more lamina such as described in US Pat. No. 6,210,712.

**[000235]** Preferably, the semi-permeable wall 20 comprises a polymer selected from the group consisting of cellulose acetate and cellulose acetate butyrate.

**[000236]** Semi-permeable wall 20 may further, optionally, comprise a flux-regulating agent. The flux regulating agent is a compound added to assist in regulating the water permeability or flux through semi-permeable wall 20. The flux-regulating agent can be a flux-enhancing agent or a flux-decreasing agent. The flux-regulating agent can therefore be pre-selected to increase or

decrease the flux of the external water through the semi-permeable membrane. Flux-regulating agents that produce a marked increase in permeability to fluid such as water are often essentially hydrophilic, while those that produce a marked decrease to fluids such as water are essentially hydrophobic. The amount of flux-regulator in semi-permeable wall 20 when incorporated therein is preferably in the range of from about 0.01% to about 25% by weight or more.

**[000237]** Suitable flux-regulating agents include, but are not limited to, polyhydric alcohols, polyalkylene glycols, polyalkylenediols, polyesters of alkylene glycols, and the like.

**[000238]** Flux enhancers include, but are not limited to, polyethylene glycol 300, 400, 600, 1500, 4000, 6000 and the like; low molecular weight glycols such as polypropylene glycol, polybutylene glycol and polyamylene glycol; the polyalkylenediols such as poly(1,3-propanediol), poly(1,4-butanediol), poly(1,6-hexanediol), and the like; aliphatic diols such as 1,3-butylene glycol, 1,4-pentamethylene glycol, 1,4-hexamethylene glycol, and the like; alkylene triols such as glycerine, 1,2,3-butanetriol, 1,2,4-hexanetriol, 1,3,6-hexanetriol and the like; esters such as ethylene glycol dipropionate, ethylene glycol butyrate, butylene glycol dipropionate, glycerol acetate esters, and the like. Preferred flux enhancers include the group of difunctional block-copolymer of ethylene oxide and propylene oxide conforming to the general formula  $\text{OH}(\text{C}_2\text{H}_4\text{O})_a(\text{C}_3\text{H}_6\text{O})_b(\text{C}_2\text{H}_4\text{O})\text{H}$ , known as PLURONIC<sup>®</sup> co-polymers (sold in pharmaceutical grade under the trade name LUTROL).

**[000239]** Flux-decreasing agents include, but are not limited to, phthalates substituted with an alkyl or alkoxy or with both an alkyl and alkoxy group such as diethyl phthalate, dimethoxyethyl phthalate, dimethyl phthalate, and [di(2-ethylhexyl) phthalate], aryl phthalates such as triphenyl phthalate, and butyl benzyl phthalate; polyvinyl acetates, triethyl citrate, Eudragit; insoluble salts such as calcium sulfate, barium sulfate, calcium phosphate, and the like; insoluble oxides such as titanium oxide; polymers in powder, granule and like form such as polystyrene, polymethylmethacrylate, polycarbonate, and polysulfone; esters such as citric acid esters esterified with long chain alkyl

groups; inert and substantially water impermeable fillers; resins compatible with cellulose based wall forming materials, and the like.

**[000240]** Other materials may be further, optionally, included in the semi-permeable wall composition for imparting flexibility and / or elongation

5 properties, i.e. to make semi-permeable wall 20 less brittle and / or to render tear strength to semi-permeable wall 20. Suitable materials include, but are not limited to, phthalate plasticizers such as dibenzyl phthalate, dihexyl phthalate, butyl octyl phthalate, straight chain phthalates of six to eleven carbons, di-isononyl phthalate, di-isodecyl phthalate, and the like. Plasticizers  
10 include nonphthalates such as triacetin, dioctyl azelate, epoxidized tallate, triisooctyl trimellitate, tri-isononyl trimellitate, sucrose acetate isobutyrate, epoxidized soybean oil, and the like. The amount of plasticizer in semi-permeable wall 20 when incorporated therein is preferably in the range of from about 0.01% to about 20% weight, or higher.

15 **[000241]** Exit orifice 60 is provided in each osmotic dosage form. Exit 60 may encompass one or more exit orifices. Exit 60 cooperates with the drug composition(s) within the dosage form for the uniform release of drug from the dosage form. The exit can be provided during the manufacture of the dosage form or during drug delivery by the dosage form in a fluid environment of use.

20 **[000242]** Exit 60 may include an orifice that is formed or formable from a substance or polymer that erodes, dissolves or is leached from the outer wall to thereby form an exit orifice. The substance or polymer may include, for example, an erodible poly(glycolic) acid or poly(lactic) acid in the semi-permeable wall; a gelatinous filament; a water-removable poly(vinyl alcohol); a  
25 leachable compound, such as a fluid removable pore-former selected from the group consisting of inorganic and organic salt, oxide, carbohydrate, and the like.

**[000243]** The exit 60, or a plurality of exits, can alternatively be formed by leaching a member selected from the group consisting of sorbitol, lactose,  
30 fructose, glucose, mannose, galactose, talose, sodium chloride, potassium chloride, sodium citrate and mannitol to provide a uniform-release dimensioned pore-exit orifice.

**[000244]** Exit 60 can have any shape, such as round, triangular, square, oval, elliptical, and the like, for the uniform metered dose release of a drug from the dosage form.

5 **[000245]** When more than one exit orifice is present in the dosage form, the exits may be present in spaced-apart relation on one or more surfaces of the dosage form, provided that the exit orifices are situated such that they expose drug composition to the external environment.

10 **[000246]** The drug compositions of the present invention may be prepared according to known methods, for example as a granulation, as a dry blend, as a co-precipitate, as a roller compacted blend, and the like. Preferably, the drug composition is prepared as a granulation.

15 **[000247]** A variety of processing techniques can be used to promote uniformity of mixing between the pharmaceutical agent 31 and solubilizing agent, preferably surfactant, 33 in drug composition 30. In one method, the drug and surfactant are each micronized to a nominal particle size of less than about 200 microns, preferably, to a nominal particle size of less than about 100 microns, more preferably, to a nominal particle size of less than about 50 microns. Standard micronization processes such as jet milling, cryogrinding, bead milling, and the like, may be used.

20 **[000248]** Alternatively, the drug and solubilizing agent may be dissolved in a common solvent to produce mixing at the molecular level and co-dried to a uniform mass. The resulting mass may be ground and sieved to a free-flowing powder. The resulting free-flowing powder may be further, optionally, granulated with wet mass sieving or fluid bed granulation with any optional structural polymer to form a drug composition (in the form of a granulation) of  
25 the present invention.

30 **[000249]** Alternatively still, pharmaceutical agent 31 and solubilizing agent 33 may be melted together at elevated temperature to mix the drug in solubilizing agent, preferably surfactant, and then congealed to room temperature. The resulting solid may be ground, sized, and optionally, further granulated with structural polymer.

**[000250]** In yet another manufacturing process, pharmaceutical agent 31 and solubilizing agent 33 may be dissolved in a common solvent or blend of

solvents and spray dried to form a co-precipitate that is then further, optionally incorporated with structural polymer by standard granulation processing by fluid bed processing or wet mass sieving.

5     **[000251]**     In yet another manufacturing process, pharmaceutical agent 31 and solubilizing agent 33 may be dissolved in a common solvent or blend of solvents which pharmaceutical agent/surfactant solution is then sprayed onto the optional structural polymer directly in a fluid bed granulation process.

10     **[000252]**     The drug composition of the present invention may then be formulated into the dosage forms of the present invention. Drug composition 30 within the dosage form is preferably formed by compression of the pharmaceutical agent 31, solubilizing agent 33, preferably surfactant, and if present, the structural polymer 32. For the preparation of osmotic dosage forms, one or more drug compositions are compressed in a stacked orientation, with a push layer prepared and incorporated into the dosage form in contacting relation to at least one of the drug compositions.

15     **[000253]**     Each drug composition is prepared by mixing the pharmaceutical agent 31 with the solubilizing agent 33 and any additional components (e.g. structural polymer 32) into a uniform mixture.

20     **[000254]**     Alternatively, the drug composition 30 may be formed from particles by comminution that produces the size of the pharmaceutical agent and the size of any accompanying polymers used in the fabrication of the drug composition, typically as a core containing the compound. Means for producing such particles include, but are not limited to, granulation, spray drying, sieving, lyophilization, crushing, grinding, jet milling, micronizing and chopping to produce the intended micron particle size. The process can be performed by size reduction equipment, such as a micropulverizer mill, a fluid energy grinding mill, a grinding mill, a roller mill, a hammer mill, an attrition mill, a chaser mill, a ball mill, a vibrating ball mill, an impact pulverizer mill, a centrifugal pulverizer, a coarse crusher, a fine crusher, and the like. The size of the particle(s) can be ascertained by screening, including a grizzly screen, a flat screen, a vibrating screen, a revolving screen, a shaking screen, an oscillating screen, a reciprocating screen and the like. The processes and equipment for preparing drug and / or carrier particles are disclosed in

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Remington's Pharmaceutical Sciences, 18th Ed., pp. 1615-1632 (1990);  
Chemical Engineers Handbook, Perry, 6th Ed., pp. 21-13 to 21-19 (1984);  
Journal of Pharmaceutical Sciences, Parrot, Vol. 61, No. 6, pp. 813-829  
(1974); and Chemical Engineer, Hixon, pp. 94-103 (1990).

5     **[000255]**     Exemplary solvents suitable for manufacturing drug compositions  
and / or the push layer for the dosage form comprise aqueous or inert organic  
solvents that do not adversely harm the materials used in the system. Such  
solvents include, but are not limited to, members selected from the group  
consisting of aqueous solvents, alcohols, ketones, esters, ethers, aliphatic  
10    hydrocarbons, halogenated solvents, cycloaliphatics, aromatics, heterocyclic  
solvents and mixtures thereof. Suitable examples of solvents include, but are  
not limited to, acetone, diacetone alcohol, methanol, ethanol, isopropyl alcohol,  
butyl alcohol, methyl acetate, ethyl acetate, isopropyl acetate, n-butyl acetate,  
methyl isobutyl ketone, methyl propyl ketone, n-hexane, n-heptane, ethylene  
15    glycol monoethyl ether, ethylene glycol monoethyl acetate, methylene  
dichloride, ethylene dichloride, propylene dichloride, carbon tetrachloride  
nitroethane, nitropropane tetrachloroethane, ethyl ether, isopropyl ether,  
cyclohexane, cyclooctane, benzene, toluene, naphtha, tetrahydrofuran,  
diglyme, water, aqueous solvents containing inorganic salts such as sodium  
20    chloride, calcium chloride, and the like, and mixtures thereof such as acetone  
and water, acetone and methanol, acetone and ethyl alcohol, methylene  
dichloride and methanol, and ethylene dichloride and methanol.

**[000256]**     Push layer 40 may be similarly prepared according to known  
methods, for example according to the processes described above, by mixing  
25    the appropriate ingredients under appropriate conditions (e.g. osmoagent,  
omsopolymer, etc.).

**[000257]**     Semi-permeable wall 20 may be similarly prepared according to  
known methods, for example by pan coating, by mixing the appropriate  
ingredients and applying the resulting mixture to dosage form.

30    **[000258]**     Dosage form components (e.g. drug composition(s), push layer,  
semi-permeable wall, exit orifice, etc.) may be combined to form the dosage  
forms of the present invention according to standard techniques known in the  
art. More specifically, the dosage form core, comprising one or more drug

compositions, and when present the push layer, is prepared first, preferably by compression. The semi-permeable wall is then coated onto the core and one or more exit orifices are provided through the semi-permeable wall to expose one or more drug compositions to the external environment.

5     **[000259]**     For example, the dosage form may be manufactured by the wet granulation technique. In the wet granulation technique, the drug, optional structural polymer and solubilizing agent, preferably surfactant, are blended using an organic solvent, such as denatured anhydrous ethanol, as the granulation fluid. Any additional excipients can then be dissolved in a portion  
10     of the granulation fluid, such as the solvent described above, and this latter prepared solution is slowly added to the drug blend with continual mixing in the blender. The granulating fluid is added until a wet blend is produced, which wet mass blend is then forced through a predetermined screen onto oven trays. The blend is dried for 18 to 24 hours at 24°C to 35°C in a forced-air  
15     oven. The dried granules are then sized. Next, magnesium stearate, or another suitable lubricant, is added to the drug granulation, and the granulation is put into milling jars and mixed on a jar mill for up to 10 minutes. The composition is pressed into a layer, for example, in a Manesty® press or a Korsch LCT press.

20     **[000260]**     For a bi-layered core (i.e. a dosage form which comprises a drug composition and a push layer), the drug composition is pressed and a similarly prepared granulation of the push layer is pressed against the drug composition. This intermediate compression typically takes place under a force of about 50-100 newtons. Final stage compression typically takes place at a force of 3500  
25     newtons or greater, often 3500-5000 newtons.

30     **[000261]**     Wherein the core comprises two or more drug compositions and a push layer, each drug composition, prepared as described above is individually compressed. The push layer is then pressed against at least one of the drug compositions, in an intermediate compression step as described above. Final compression of the multi-layer core is then applied as described above.

**[000262]** Single, bi-layer or multi-layer compressed cores are then fed to a dry coater press, e.g., Kilian® Dry Coater press, and subsequently coated with the semi-permeable wall materials, according to known methods.

**[000263]** In another process of manufacture the drug and other ingredients comprising the drug composition are blended and pressed into a solid layer. The layer possesses dimensions that correspond to the internal dimensions of the area the layer is to occupy in the dosage form, and it also possesses dimensions corresponding to the push layer, if included, for forming a contacting arrangement therewith. The drug and other ingredients can also be blended with a solvent and mixed into a solid or semisolid form by conventional methods, such as ballmilling, calendering, stirring or rollmilling, and then pressed into a preselected shape. Next, if included, the push layer components are placed in contact with the drug composition in a like manner. The layering of the drug composition(s) and the push layer can be fabricated by conventional two-layer press techniques. The compressed cores may then be coated with the semi-permeable wall material, according to known methods.

**[000264]** Another manufacturing process that can be used comprises blending the powdered ingredients for each layer in a fluid bed granulator. After the powdered ingredients are dry blended in the granulator, a granulating fluid, for example, poly(vinylpyrrolidone) in water, is sprayed onto the powders. The coated powders are then dried in the granulator. This process granulates all the ingredients present therein while adding the granulating fluid. After the granules are dried, a lubricant, such as stearic acid or magnesium stearate, is mixed into the granulation using a blender e.g., V-blender or tote blender. The granules are then pressed in the manner described above.

**[000265]** Pan coating may be conveniently used to provide semi-permeable wall of the completed osmotic dosage forms. In the pan coating system, the wall-forming composition (comprising the semi-permeable polymer and optional, additional materials) is deposited by successive spraying of the appropriate wall composition onto the compressed single, bi-layered or multi-layered core (which core comprises the drug layer(s) and, where present, the push layer), accompanied by tumbling in a rotating pan. A pan coater is often used because of its availability at commercial scale.

**[000266]** Other known coating techniques may alternatively be used for coating the compressed core. For example, semi-permeable wall 20 of the dosage form may be formed in one technique using the air-suspension procedure. This procedure consists of suspending and tumbling the  
5 compressed single, bi-layer or multi-layer core in a current of warmed air and the semi-permeable wall forming composition, until the semi-permeable wall is applied to the core. The air-suspension procedure is well suited for independently forming the semi-permeable wall of the dosage form. The air-suspension procedure is described in U.S. Patent No. 2,799,241; in J. Am.  
10 Pharm. Assoc., Vol. 48, pp. 451-459 (1959); and, ibid., Vol. 49, pp. 82-84 (1960). The dosage form may alternatively be coated with a Wurster<sup>®</sup> air-suspension coater using, for example, methylene dichloride methanol as a cosolvent for the wall forming material. An Aeromatic<sup>®</sup> air-suspension coater may alternatively be used employing a suitable co-solvent.

15 **[000267]** Once coated, semi-permeable wall 20 is dried in a forced-air oven or in a temperature and humidity controlled oven to free the dosage form of any solvent(s) used in the manufacturing. Drying conditions are conventionally chosen on the basis of available equipment, ambient conditions, solvents, coatings, coating thickness, and the like.

20 **[000268]** Preferably, the drug compositions, the push layer and / or the dosage forms are dried to remove volatile organic and in-organic solvents to levels that are pharmaceutically acceptable and / or optimal for manufacturing. More preferably, the drug compositions, the push layer and / or the dosage forms are to less than about 10% moisture, more preferably still, to less than  
25 about 5% moisture, most preferably less than about 3% moisture.

**[000269]** One or more exit orifices are provided according to known methods, for example by drilling, in the drug composition end of the dosage form. Alternatively, one or more exit orifices may be provided in the drug composition end of the dosage form by erosion or leaching.

30 **[000270]** The dosage form can therefore be constructed with one or more exits in spaced-apart relation on one or more surfaces of the dosage form.

**[000271]** Drilling, including mechanical and laser drilling, through the semi-permeable wall can be used to form the exit orifice. Such exits and equipment

for forming such exits are disclosed in U.S. Patents Nos. 3,916,899, by Theeuwes and Higuchi and in U.S. Patent No. 4,088,864, by Theeuwes, et al.

**[000272]** Leachable or erodable exit orifices may be formed or formable from a substance or polymer that erodes, dissolves or is leached from the outer  
5 semi-permeable (outer) wall to thereby form an exit orifice. The substance or polymer may include for example, an erodible poly(glucolic)acid or poly(lactic)acid in the semi-permeable wall, a gelatinous filament, a water removable poly(vinyl)alcohol, a leachable compound such as a fluid removable pore former, for example an inorganic or organic salt, oxide or carbohydrate.

10 The exit or plurality of exits can be formed by leaching a member selected from the group consisting of sorbitol, lactose, fructose, glucose, mannose, galactose, talose, sodium chloride, potassium chloride, sodium citrate and mannitol to provide a uniform release dimensioned pore exit orifice. The exit can have any shape, such as, round, triangular, square, elliptical, and the like.

15 **[000273]** The dosage form may be further, optionally coated with additional water soluble overcoats, which may be colored (e.g., OPADRY colored coatings) or clear (e.g., OPADRY Clear).

**[000274]** The dosage form may further, optionally comprise a smoothing coat, which smoothing coat is applied to the compressed drug core, according  
20 to known methods, prior to the application of the semi-permeable wall.

Suitable examples of formulations and components which may be used in the smoothing coat include, but are not limited to, hydroxypropylcellulose, hydroxyethylcellulose, methylcellulose, hydroxypropyl methylcellulose, and the like. The coating may further optionally contain polyethylene glycol of 400 to  
25 6000 molecular weight, polyvinyl pyrrolidone of 2500 to 1,000,000 molecular weight, and the like.

**[000275]** The dosage forms of the present invention provide controlled release of pharmaceutical agent, preferably topiramate, over a prolonged period of time, preferably, for greater than about 1 hour, more preferably, for at  
30 least about 4 hours, more preferably still, for at least about 8 hours, more preferably, for at least about 10 hours, more preferably still, for at least about 14 hours, more preferably still, for at least 18 hours, more preferably still, for at least 20 hours, more preferably still for at least 22 hours, more preferably still



for up to about 24 hours. Preferably, the dosage forms of the present invention provide controlled release of pharmaceutical agent for about 2 to about 24 hours, more preferably, for about 4 to about 24 hours.

5     **[000276]**     In an embodiment of the present invention, the release of drug from the dosage forms of the present invention provides efficacious therapy for about 24 hours. In another embodiment of the present invention, the dosage form releases drug for about 16 to about 24 hours after administration.

10     **[000277]**     In an embodiment of the present invention, the dosage form comprises an optional immediate release drug overcoat which provides immediate drug delivery (i.e. within less than about 1 hour after administration) and controlled drug delivery continuing thereafter until the dosage form ceases to release drug, preferably, at least about 8 hours, more preferably, about 12 hours, more preferably still, about 16 hours, more preferably still about 18 hours, more preferably still, about 22 hours, more preferably still, about 24  
15     hours.

20     **[000278]**     Representative dosage forms of the present invention exhibit  $T_{70}$  values of greater than about 8 hours, preferably, greater than about 10 hours, more preferably, greater than about 12 hours, more preferably still, greater than about 16 hours, and release drug, preferably topiramate, for a continuous period of time of more than about 12 hours, more preferably, for more than about 16 hours, more preferably still, for about 24 hours.

25     **[000279]**     Within about 2 hours following administration, representative dosage forms of the present invention release drug, preferably topiramate, at a substantially zero order rate of release or at a substantially ascending rate of release, depending upon the composition of drug composition(s) and push layers. Preferably, drug release continues for a prolonged period of time. Following the prolonged period of delivery, drug continues to be delivered for several more hours until the dosage form is spent or expelled from the GI tract.

30     **[000280]**     In a bi-layer embodiment of once-a-day dosage forms in accord with the present invention, the dosage forms have a  $T_{70}$  of about 15 hours to about 18 hours, preferably, about 17 hours, and provided release of drug, preferably topiramate, for a continuous period of time, preferably, for at least

about 24 hours. Preferably, the dosage form releases drug with a substantially zero order rate of release.

5 [000281] In a tri-layer embodiment of the present invention, the dosage form of the present invention comprises two drug compositions and a push layer, wherein the amount and / or concentration of drug in the first drug composition is less than the amount and / or concentration of drug in the second drug composition. Representative tri-layer dosage forms of the present invention exhibit  $T_{70}$  values of greater than about 8 hours, preferably, greater than about 12 hours, more preferably, greater than about 14 hours, and  
10 release drug, preferably topiramate, for a continuous period of time of more than about 16 hours, preferably for about 24 hours. Preferably, the dosage form releases drug with a substantially ascending rate of release.

[000282] In an embodiment of the present invention, the dosage forms of the present invention release the pharmaceutical agent (drug) at various rates  
15 of release between about 1%/hr and about 12 %/hr over a prolonged period of time.

[000283] In an embodiment of the present invention, the dosage forms release pharmaceutical agent with a substantially zero order rate of release. In another embodiment of the present invention, the dosage forms release  
20 pharmaceutical agent with a substantially ascending rate of release. In yet another embodiment of the present invention, the dosage forms release pharmaceutical agent with a release rate which results in a substantially ascending drug plasma concentration.

[000284] The present invention is further directed to a method of treatment  
25 comprising administering any of the drug compositions or dosage forms of the present invention, to a patient in need thereof. Said drug compositions and / or dosage forms comprise pharmaceutical agent, preferably topiramate, in the range of from about 1 mg to about 750 mg.

[000285] The method, in one embodiment, comprises administering orally  
30 to a patient in need thereof, a pharmaceutical agent, preferably topiramate, administered from a dosage form comprising the desired amount of said pharmaceutical agent and solubilizing agent, preferably surfactant.

**[000286]** The present invention further provides methods for administering pharmaceutical agent, preferably topiramate, to a patient, and methods for producing a desired drug plasma concentration of topiramate. In an embodiment of the present invention is a method for administering orally to a patient in need thereof, a dosage form that administers at a controlled rate, over a continuous period of time up to about 24 hours, drug for its intended therapy. In another embodiment of the present invention, the method comprises administering orally to a patient in need thereof, a therapeutic dose of pharmaceutical agent, preferably topiramate, from a single dosage form that administers the topiramate over about 24 hours.

**[000287]** The present invention is further directed to a method of treatment comprising administering to a patient in need thereof, an oral controlled release dosage form of a pharmaceutical agent, preferably topiramate, wherein the pharmaceutical agent is released from the dosage form in a substantially zero order rate of release.

**[000288]** The present invention is further directed to a method of treating comprising administering to a patient in need thereof, an oral controlled release dosage form of a pharmaceutical agent, preferably topiramate, wherein the pharmaceutical agent is released from the dosage form in a substantially ascending rate of release.

**[000289]** The present invention is further directed to a method of treating comprising administering to a patient in need thereof, an oral controlled release dosage form of a pharmaceutical agent, preferably topiramate, wherein the pharmaceutical agent is released from the dosage form at a rate which results in a substantially ascending drug plasma concentration.

**[000290]** The present invention is further directed to a method of treating a disorder is selected from the group consisting of epilepsy, migraine, glaucoma and other ocular disorders (including diabetic retinopathy), essential tremor, restless limb syndrome, obesity, weight loss, Type II Diabetes Mellitus, Syndrome X, impaired oral glucose tolerance, diabetic skin lesions, cluster headaches, neuralgia, neuropathic pain (including diabetic neuropathy), elevated blood glucose levels, elevated blood pressure, elevated lipids, bipolar disorder, dementia, depression, psychosis, mania, anxiety, schizophrenia,

OCD, PTSD, ADHD, impulse control disorders (including bulimia, binge eating, substance abuse, etc.), ALS, asthma, autism, autoimmune disorders (including psoriasis, rheumatoid arthritis, etc.), chronic neurodegenerative disorders, acute neurodegeneration, sleep apnea and other sleep disorders or for promoting wound healing, comprising administering to a patient in need thereof, any of the drug compositions or dosage forms of the present invention.

5 [000291] Preferably, the disorder is selected from the group consisting of epilepsy, migraine, diabetic retinopathy, diabetic neuropathy, diabetic skin lesions, obesity, weight loss, Type II Diabetes Mellitus, Syndrome X, impaired  
10 oral glucose tolerance, elevated blood glucose levels and elevated blood pressure.

[000292] The following examples are illustrative of the present invention and should not be considered as limiting the scope of the invention in any way, as these examples and other equivalents thereof will become apparent to  
15 those versed in the art in light of the present disclosure, drawings and accompanying claims.

### **Example 1**

#### **Bi-Layered Osmotic Dosage Form of Topiramate**

20 [000293] A drug composition of the present invention was prepared as follows. Aqueous solutions of five surfactants were prepared. The selected surfactants were four grades of ethylene oxide/propylene oxide/ethylene oxide (LUTROL grades F127, F87, F 108, and F68) and PEG-40 stearate (MYRJ 52). Solutions were made at concentrations of 1, 5, and 15 weight percent.  
25 The aqueous surfactant blends solutions were chilled as necessary to promote complete dissolution of the surfactant prior to drug solubility studies. Each surfactant had a different HLB value and spanned a range of 16.9 to 29 HLB units.

[000294] The aqueous surfactant solutions were equilibrated to constant  
30 temperature in a 37°C water bath. Then, neat topiramate drug was added slowly with stirring in approximately 10 mg increments to the surfactant solutions until no more drug dissolved. A control sample of drug dissolved in de-ionized water without surfactant was included for comparison purposes.

The resulting saturated solutions of drug were filtered through 0.8 micron filters and analyzed for drug concentration by refractive index chromatography. The resulting solubility values were plotted as a function of both surfactant concentration and the hydrophilic-lipophilic balance value of each surfactant.

5 Figure 6 was constructed from the solubility values obtained and HLB data for each surfactant utilized.

[000295] This method revealed three insights. Referring to Figure 6, topiramate solubility in water was increased by each surfactant. Drug solubility was higher in the presence of each surfactant compared to the control where  
10 the solubility in de-ionized water without surfactant was 13.0 mg/ml. Second, a high concentration of surfactant was more effective in solubilizing drug than a low concentration. Third, the HLB values most effective to increase solubility of this drug were at the lower end, in the range of 16.9 to 22. The three concentrations of surfactant each formed the maximal solubility of topiramate  
15 with an HLB encompassing this range of HLB values.

[000296] Following this finding, a drug composition of the present invention was prepared. First, 55 grams of topiramate, 30 grams of granular LUTROL F 127, 11.5 grams of the polyethylene oxide (PEO) N80, and 3 grams of polyvinyl pyrrolidone (PVP) 2932 were passed through a #40 mesh sieve and the  
20 composition was dry mixed to a uniform blend wherein the PVP acts as a binder and the PEO acts as the structural polymer (carrier). The molecular weight of the polyethylene oxide was 200,000 grams per mole and the molecular weight of the polyvinyl pyrrolidone was approximately 10,000. The polyoxyethylene oxide serves as carrier and structural polymer 32. The  
25 polyvinyl pyrrolidone serves as the drug layer binder 36. The dry mixture was then wetted with anhydrous ethyl alcohol SDA 3A anhydrous and stirred to form a uniformly wetted mass. The wet mass was then passed through a 20-mesh sieve, forming damp noodles. The noodles were air dried at ambient conditions overnight, then passed again through a #20 mesh sieve, forming  
30 free-flowing granules. Finally, 0.5 grams of drug layer lubricant 34 magnesium stearate was passed through a # 60 mesh sieve over the granules and tumble mixed into the granules. This formed the drug composition granulation.



**[000297]** A push layer granulation was prepared in a similar manner. First, 89 grams of polyethylene oxide 303, 7 grams of sodium chloride, and 3 grams of hydroxypropyl methylcellulose E5 were passed through a #40 mesh sieve and dry mixed. The polyethylene oxide had a molecular weight of approximately 7,000,000 and the hydroxypropyl methylcellulose had a molecular weight of approximately 11,300. The polyethylene oxide served as the push layer osmopolymer 41 and the hydroxypropyl methylcellulose provided the push layer binder 43. Next, the dry mixture was wetted with anhydrous ethyl alcohol SDA 3A and mixed to a uniform damp mass. The mass was passed through a #20 mesh sieve forming noodles that were air dried overnight. Next, the noodles were passed again through a #20 mesh sieve forming free-flowing granules. Finally, 0.5 grams of minus #60 mesh magnesium stearate, push layer lubricant 44, was tumbled into the blend. This formed the push layer granulation.

**[000298]** A portion of the drug composition granulation weighing 182 mg was filled into a 3/16 inch diameter die cavity and lightly tamped with 3/16 inch biconvex round tablet tooling. Then, 60 mg of the push layer granulation was filled into the die and compressed and laminated to the drug layer using a force of 0.5 tons with a Carver press. Six of these bi-layer tablets were compressed.

**[000299]** Next, the tablets were coated with three layers. First, a solution was prepared by dissolving 57 grams of hydroxyethyl cellulose 250L and 3 grams of polyethylene glycol in 940 grams of de-ionized water. The hydroxyethyl cellulose had a molecular weight of approximately 90,000 and the polyethylene glycol had a molecular weight of 3,350. This formed a smoothing coat solution to provide a smooth coatable surface for subsequent coatings.

**[000300]** The six active tablets were mixed into a tablet bed of placebo tablets that weighed 0.5 kg. The tablet bed was coated with the smoothing coat solution in an Aeromatic coater. The solution was applied in a current of warm, dry air until approximately 4 mg of coating weight was accumulated on each active tablet. The coating solution was stirred continuously during the coating process. The resulting smoothing coat produced a smooth tablet substrate and rounded the corners of the tablets. The resulting smooth tablets were dried in a 40°C force air oven overnight. (This smoothing coat is optional

and is especially useful to round the corners of the tablets where tablet lands have flash from the compression process.)

5 [000301] The next coating solution was prepared by dissolving 269.5 grams of ethyl cellulose 100 cps, 196.0 grams of hydroxypropyl cellulose EFX, and 24.5 grams of MYRJ 52 in 6510 grams of anhydrous ethanol SDA3A with stirring and warming. The ethyl cellulose had a molecular weight of approximately 220,000 and the hydroxypropyl cellulose had a molecular weight of approximately 80,000. The solution was allowed to stand at ambient temperature. This formed the membrane subcoat solution.

10 [000302] The smooth tablets from above were mixed into a bed of placebo tablets weighing 1.2 kg and the resulting mixed bed was charged into a Vector LDCS pan coater fitted with a 14 inch diameter coating pan. The membrane subcoat solution was then sprayed onto the bed of tablets in the coater in a current of warm air. The coating solution was stirred continuously during the process. The solution was applied in this manner until approximately 5.5 mils of coating was accumulated on each drug tablet.

15 [000303] Then, 175 grams of cellulose acetate 398-10 and 75 grams of LUTROL F68 were dissolved in 4,750 grams of acetone with warming and stirring. The cellulose acetate had an average acetyl content of approximately 39.8 weight percent and a molecular weight of approximately 40,000. This formed the membrane overcoat solution.

20 [000304] This membrane overcoat solution was applied to the bed of active and placebo cores in the LDCS pan coater until 5 mils of membrane overcoat accumulated on each drug tablet. The three-coated layers formed wall 20 of the present invention. An exit orifice 60 was mechanically drilled through the three coating layers on the drug layer side of the tablets using a 40 mil diameter drill bit and drill press. The systems were then dried in a forced air oven at 40°C to remove residual processing solvents.

25 [000305] The resulting six dosage forms (systems) were tested for release of drug as a function of time in de-ionized water at 37°C by sampling every 2 hours over a duration of 24 hours. Drug release was monitored with refractive index chromatography. The resulting release pattern of drug was as shown in Figure 7. The drug 31 was delivered at an ascending release pattern for 12-14

hours. The time to deliver 90% of the 100 mg dose was approximately 18 hours. The cumulative delivery at 24 hours was 97.5%. The membranes were intact throughout the delivery pattern.

5 [000306] The dosage forms were sufficiently small to easily be swallowed by a patient even with the high drug loading of 55% present in the drug composition 30.

[000307] Similar dosage forms with push layers were formulated with 55% drug in the drug composition, but without the solubilizing surfactant in an attempt to implement prior art technology. These dosage forms of the prior art  
10 were not operational. The drug compositions representing the prior art did not solublize the drug and resulted in drug compositions that could not be pumped from the dosage forms. The membranes of these dosage forms split open in situ during in vitro testing, dumping the bolus of drug in an uncontrolled fashion. The splitting of the dosage forms was due to the strain induced within  
15 the membrane by the swelling pressure generated by the push layer pushing against the insoluble drug composition through the narrow 40 mil port.

### Example 2

#### Bi-Layered Topiramate Dosage Form

20 [000308] A drug composition of 9.0 grams of micronized LUTROL F 127 was dry mixed with 16.5 grams of topiramate. The topiramate had a nominal particle size of 80 microns. Next, 3.45 grams POLYOX N80 and 0.9 grams of polyvinyl pyrrolidone were sieved through a minus 40 mesh and blended into the mixture. Then, 5 grams of anhydrous ethanol was added slowly with  
25 stirring to form a damp mass. The damp mass was passed through a #16 mesh sieve and air dried overnight at ambient temperature. The resulting dried noodles were passed again through #16 mesh sieve. Then, 150 mg of magnesium stearate was passed through a #60 mesh sieve over the dried granules and tumble mixed into the granules. The concentration of surfactant  
30 in this drug composition granulation was 30 weight percent

[000309] The push layer granulation was prepared by passing 63.67 grams of POLYOX 303, 30 grams of sodium chloride, and 5 grams of hydroxypropyl methyl cellulose through a #40 mesh sieve and dry mixing to form a uniform

blend. Then, 1.0 gram of ferric oxide red was passed through a #60 mesh sieve into the mixture. The resulting mixture was wet massed by slowly adding anhydrous ethyl alcohol SDA3A anhydrous with stirring to form a uniformly damp mass. The mass was passed through a # 20 mesh sieve, resulting in noodles that were dried at 40°C in forced air overnight. The dried noodles were passed through a # 16 mesh sieve to form free-flowing granules. Finally, 25 mg of magnesium stearate and 8 mg of butylated hydroxytoluene were sieved through a # 80 mesh sieve into the granules and tumble mixed.

**[000310]** A portion of the drug composition granulation weighing 182 mg was filled into a round 3/16-inch diameter die and lightly compressed with 3/16-inch concave punches. Then, 60 mg of the push layer granulation was added to the drug layer and the two layers were laminated with a force of 800 pounds. Six tablets were made.

**[000311]** The tablets were coated as described in Example 1 with 5 mg of the smoothing coat, 5.4 mils of the subcoat membrane, and 5.7 mils of the overcoat membrane. One exit port of 40 mils diameter was drilled through the three coating layers and the systems were dried overnight at 40°C in forced air.

**[000312]** The resulting dosage forms were tested as described in Example 1. The release profile of topiramate is shown in Figure 8. The systems released 99% of the drug over a 24 hour duration. The release rate was substantially ascending during the first 14 hours over which time about 76% of the drug was released. The system released approximately 90 % of the drug over 19 hours. The final system was of the same size that is convenient and feasible for patients in need to swallow as described in Example 1.

### **Example 3**

#### **Bi-Layered Topiramate Dosage Forms**

**[000313]** Systems were made as described in Example 2 except that the surfactant 33 comprised a blend of two solubilizing surfactants. The drug composition granulation was made according to the procedure in Example 2 except that the surfactant consisted of 15 weight percent micronized LUTROL F127 and 15 weight percent MYRJ 52 substituted for the 30 weight percent micronized LUTROL F127. The weighted average HLB value of the two

surfactants yielded an HLB value of 19.5, that is mid point between the two HLB values of the single surfactants.

5     **[000314]**     The delivery pattern of the resulting dosage forms is shown in Figure 10. The dosage forms delivered at a substantially zero order rate between hour 2 and hour 14. The dosage forms released 89% of the dose over 24 hours.

#### **Example 4**

##### **Bi-Layered Topiramate Dosage Forms**

10     **[000315]**     Dosage forms were made as described in Example 3 but with a larger weight of the push layer. The push layer weight was 90 mg substituted for the 60 mg weight of the systems in Example 3

15     **[000316]**     The delivery pattern of the resulting dosage form was shown in Figure 9. The system delivered at a substantially ascending release rate for about 12 hours. After 12 hours, the rate became descending. The amount of drug delivered over 24 hours was about 93%.

#### **Example 5**

##### **Bi-Layered Topiramate Dosage Form**

20     **[000317]**     A drug composition 30 was formed consisting of 30 wt % drug topiramate, 56 wt % surfactant LUTROL F127, 10 wt% carrier POLYOX N80 and 3 wt% PVP K2932 and 2 wt% stearic acid by wet granulating with anhydrous ethanol.

25     **[000318]**     A push layer consisting of 63.37 wt% POLYOX 303 (7,000,000 molecular weight), 30 wt% NaCl, 5 wt% HPMC E5, 1 wt% Ferric Oxide, 0.5 wt% Mg Stearate and 0.08 wt% BHT was wet granulated with anhydrous ethanol.

30     **[000319]**     Tablets with 333 mg of the drug composition (100 mg topiramate) and 133 mg push layer were compressed using a 9/32" longitudinally compressed tablet tooling. Total tablet (capsule shape) weight was 466 mg. The systems were coated, drilled, and dried according to the procedures described in Example 1. The systems were then tested for release of drug,



producing a substantially zero order release pattern, delivering the drug at a steady rate of about 5.8 mg per hour over approximately 16 hours.

### **Example 6**

#### **Topiramate Capsule Shaped Tri-layer 100 mg System**

5                   **[000320]**       A first drug composition was prepared as follows. First, 3000 g of topiramate, 2520 g of polyethylene oxide with average molecular weight of 200,000 and 3630 g of poloxamer 407 (LUTROL F127) having an average molecular weight of 12,000 were added to a fluid bed granulator bowl. Next  
10       two separate binder solutions, a poloxamer binder solution and a polyvinylpyrrolidone identified as K29-32 having an average molecular weight of 40,000 binder solution were prepared by dissolving 540 g of the same poloxamer 407 (LUTROL F127) in 4860 g of water and 495 g of the same polyvinylpyrrolidone in 2805 of water, respectively. The dry materials were fluid  
15       bed granulated by first spraying with 2700 g of the poloxamer binder solution and followed by spraying 2000 g of the polyvinylpyrrolidone binder solution. Next, the wet granulation was dried in the granulator to an acceptable moisture content 0.3%, and sized using by passing through a 7-mesh screen. Next, the granulation was transferred to a blender and mixed with 5 g of butylated  
20       hydroxytoluene as an antioxidant and lubricated with 200 g of stearic acid and 75 g of magnesium stearate.

**[000321]**       A second drug composition was prepared as follows. First, 4000 g of topiramate, 213 g of polyethylene oxide with average molecular weight of 200,000, 4840 g of poloxamer 407 (LUTROL F127) having an average  
25       molecular weight of 12,000 and 10 g of ferric oxide, black were added to a fluid bed granulator bowl. Next, two separate binder solutions, a poloxamer binder solution and a polyvinylpyrrolidone identified as K29-32 having an average molecular weight of 40,000 binder solution were prepared by dissolving 720 g of the same poloxamer 407 in 6480 g of water and 495 g of the same  
30       polyvinylpyrrolidone in 2805 of water, respectively. The dry materials were fluid bed granulated by first spraying with 3600 g of the poloxamer binder solution and followed by spraying 2000 g of the polyvinylpyrrolidone binder solution. Next, the wet granulation was dried in the granulator to an acceptable moisture

content, and sized by passing through a 7-mesh screen. Next, the granulation was transferred to a blender and mixed with 2 g of butylated hydroxytoluene as an antioxidant and lubricated with 200 g of stearic acid and 75 g of magnesium stearate.

5     **[000322]**     Next, a push clayer was prepared as follows. First, a binder solution was prepared. 7.5 kg of polyvinylpyrrolidone identified as K29-32 having an average molecular weight of 40,000 was dissolved in 50.2 kg of water. Then, 37.5 kg of sodium chloride and 0.5 kg of ferric oxide were sized using a Quadro Comil with a 21-mesh screen. Then, the screened materials  
10     and 80.4 kg of polyethylene oxide (approximately 7,000,000 molecular weight) were added to a fluid bed granulator bowl. The dry materials were fluidized and mixed while 48.1 kg of binder solution was sprayed from 3 nozzles onto the powder. The granulation was dried in the fluid-bed chamber to an acceptable moisture level, 0.5%. The coated granules were sized using a Fluid  
15     Air mill with a 7-mesh screen. The granulation was transferred to a tote tumbler, mixed with 63 g of butylated hydroxytoluene and lubricated with 310 g stearic acid.

20     **[000323]**     Next, the first and second drug compositions and the push layer were compressed into tri-layer tablets on multilayer Korsch press. First, 120 mg of the first drug composition was added to the die cavity and pre-compressed, then, 160 mg of the second drug composition was added to the die cavity and pre-compressed again, and finally, the push layer was added to achieve the total system weight of 480 mg and the layers were pressed into a 1/4" diameter, capsule shaped, deep concave, tri-layer arrangement.

25     **[000324]**     The tri-layer arrangements were coated with bi-layer polymer membrane laminate in which the first coating layer was a rigid yet water permeable laminate and the second coating layer was a semi-permeable membrane laminate. The first membrane laminate composition comprised 55% ethylcellulose, 45% hydroxylpropyl cellulose and 5% POLYOXYL 40  
30     stearate (PEG 40 stearate or MYRJ 52S). The membrane-forming composition was dissolved in 100% ethyl alcohol to make a 7% solids solution. The membrane-forming composition was sprayed onto and around the tri-layer

arrangements in a 10 kg scale pan coater until approximately 45 mg of membrane was applied to each tablet.

5     **[000325]**     Next, the tri-layer arrangements coated with the first membrane laminate were coated with the semi-permeable membrane. The membrane forming composition comprised 80% cellulose acetate having a 39.8% acetyl content and 20% poloxamer 188 (PLURONIC F68 or LUTROL F68). The membrane-forming composition was dissolved in 100% acetone solvent to make a 5% solids solution. The membrane-forming composition was sprayed onto and around the tri-layer arrangements in a pan coater until approximately 10     35 mg of membrane was applied to each tablet.

**[000326]**     Next, one 40 mil (1 mm) exit passageway was laser drilled through the bi-layer membrane laminate to connect the drug layer with the exterior of the dosage system. The residual solvent was removed by drying for 72 hours at 40°C and ambient humidity.

15    **[000327]**     Next, the drilled and dried systems were color overcoated. The color overcoat was a 12% solids suspension of OPADRY in water. The color overcoat suspension was sprayed onto the tri-layer systems until an average wet coated weight of approximately 25 mg per system was achieved.

**[000328]**     Next, the color-overcoated systems were clear coated. The clear coat was a 5% solids solution of OPADRY in water. The clear coat solution was sprayed onto the color coated cores until an average wet coated weight of approximately 10 mg per system was achieved.

**[000329]**     The dosage form produced by this manufacture were designed to deliver 100 mg of topiramate in a substantially ascending rate of release at 25    certain controlled-delivery rate from the core containing the first drug composition of 30% topiramate, 25.2% polyethylene oxide possessing a 200,000 molecular weight, 39% poloxamer 407 (LUTROL F127), 3% polyvinylpyrrolidone possessing a 40,000 molecular weight, 0.05% butylated hydroxytoluene, 2% stearic acid and 0.75% magnesium stearate, and the 30    second drug composition of 40% topiramate, 2.13% polyethylene oxide possessing a 200,000 molecular weight, 52% poloxamer 407 (LUTROL F127), 3% polyvinylpyrrolidone possessing a 40,000 molecular weight, 0.1% black ferric oxide, 0.05% butylated hydroxytoluene, 2% stearic acid and 0.75%

magnesium stearate. The push layer was comprised 64.3% polyethylene oxide comprising a 7,000,000 molecular weight, 30% sodium chloride, 5% polyvinylpyrrolidone possessing an average molecular weight of 40,000, 0.4% ferric oxide, 0.05% butylated hydroxytoluene (BHT), and 0.25% stearic acid.

5 The bi-layer membrane laminate in which the first membrane layer was comprised of 55% ethylcellulose, 45% hydroxylpropyl cellulose and 5% POLYOXYL 40 stearate (PEG 40 stearate or MYRJ 52S), and the second membrane laminate was a semi-permeable wall which was comprised of 80% cellulose acetate of 39.8% acetyl content and 20% poloxamer 188 (PLURONIC  
10 F68 or LUTROL F68). The dosage form comprised one passageway, 40 mils (1 mm) on the center of the drug side. The final dosage form contained a color overcoat and a clear overcoat.

[000330] The final dosage forms released such that about 90% of the drug was release with a substantially ascending rate of release over approximately  
15 16 hours, as shown in Figure 13.

### **Example 7**

#### **Topiramate Capsule Shaped Tri-layer 12.5 mg System**

[000331] A dosage form was manufactured as follows beginning with the  
20 first drug composition. First, 4 g of topiramate, 40 g of polyethylene oxide with average molecular weight of 200,000, 4 g of poloxamer 407 (LUTROL F127) having an average molecular weight of 12,000 and 1.5 g of polyvinylpyrrolidone identified as K29-32 having an average molecular weight of 40,000 were added to a beaker or mixing bowl. Next, the dry materials were mixed for 60 seconds.  
25 Then 16 mL of denatured anhydrous alcohol was slowly added to blended materials with continuous mixing for approximately 2 minutes. Next, the freshly prepared wet granulation was allowed to dry at room temperature for approximately 16 hours, and passed through a 16-mesh screen. Next, the granulation were transferred to an appropriate container, mixed and lubricated  
30 with 0.5 g of stearic acid.

[000332] Next, the second drug composition was prepared as follows: 6 g of topiramate, 35.95 g of polyethylene oxide with average molecular weight of 200,000, 6 g of poloxamer 407 (LUTROL F127) having an average molecular

weight of 12,000, 1.5 g of polyvinylpyrrolidone identified as K29-32 having an average molecular weight of 40,000 and 0.05 g of ferric oxide were added to a beaker or mixing bowl. Next, the dry materials were mixed for 60 seconds. Then 16 mL of denatured anhydrous alcohol was slowly added to blended materials with continuous mixing for approximately 2 minutes. Next, the freshly prepared wet granulation was allowed to dry at room temperature for approximately 16 hours, and passed through a 16-mesh screen. Next, the granulation were transferred to an appropriate container, mixed and lubricated with 0.5 g of stearic acid.

10 **[000333]** Next, a push layer was prepared as follows. First, a binder solution was prepared. 7.5 kg of polyvinylpyrrolidone identified as K29-32 having an average molecular weight of 40,000 was dissolved in 50.2 kg of water. Then, 37.5 kg of sodium chloride and 0.5 kg of ferric oxide were sized using a Quadro Comil with a 21-mesh screen. Then, the screened materials and 80.4 kg of polyethylene oxide (approximately 7,000,000 molecular weight) were added to a fluid bed granulator bowl. The dry materials were fluidized and mixed while 48.1 kg of binder solution was sprayed from 3 nozzles onto the powder. The granulation was dried in the fluid-bed chamber to an acceptable moisture level, 0.5%. The coated granules were sized using a Fluid Air mill with a 7-mesh screen. The granulation was transferred to a tote tumbler, mixed with 63 g of butylated hydroxytoluene and lubricated with 310 g stearic acid.

25 **[000334]** Next, the first and second drug compositions and the push layer were compressed into tri-layer tablets on the Carver Tablet Press. First, 56 mg of the first drug composition was added to the die cavity and pre-compressed, then, 67 mg of the second drug composition was added to the die cavity and pre-compressed again, and finally, the push layer was added to achieve the total system weight of 211 mg and the layers were pressed into a 3/16" diameter capsule, deep concave, tri-layer arrangement.

30 **[000335]** The tri-layer arrangements were coated with bi-layer polymer membrane laminate in which the first coating layer was a rigid yet water permeable laminate and the second coating layer was a semi-permeable membrane laminate. The coating was performed on a 10 kg scale pan coater



by spike-loading the topiramate tri-layer systems with the placebo tablets. The first membrane laminate composition comprised 55% ethylcellulose, 45% hydroxypropyl cellulose and 5% POLYOXYL 40 stearate (PEG 40 stearate or MYRJ 52S). The membrane-forming composition was dissolved in 100% ethyl alcohol to make a 7% solids solution. The membrane-forming composition was sprayed onto and around the tri-layer arrangements in a pan coater until approximately 30 mg of membrane was applied to each tablet.

**[000336]** Next, the tri-layer arrangements coated with the first membrane laminate were coated with the semi-permeable membrane. The membrane forming composition comprised 80% cellulose acetate having a 39.8% acetyl content and 20% poloxamer 188 (PLURONIC F68 or LUTROL F68). The membrane-forming composition was dissolved in 100% acetone solvent to make a 5% solids solution. The membrane-forming composition was sprayed onto and around the tri-layer arrangements in a pan coater until approximately 25 mg of membrane was applied to each tablet.

**[000337]** Next, one 30 mil (0.76 mm) exit passageway was laser drilled through the bi-layer membrane laminate to connect the drug layer with the exterior of the dosage system. The residual solvent was removed by drying for 72 hours at 40°C and ambient humidity.

**[000338]** Next, the drilled and dried systems were color overcoated. The color overcoat was a 12% solids suspension of OPADRY in water. The color overcoat suspension was sprayed onto the tri-layer systems until an average wet coated weight of approximately 15 mg per system was achieved.

**[000339]** The dosage form produced by this manufacture was designed to deliver 12.5 mg of topiramate in a substantially ascending rate of release at certain controlled-delivery rate from the core containing the first drug composition of 8% topiramate, 80% polyethylene oxide possessing a 200,000 molecular weight, 8% poloxamer 407 (LUTROL F127), 3% polyvinylpyrrolidone possessing a 40,000 molecular weight and 1% stearic acid, and the second drug composition of 12% topiramate, 71.9% polyethylene oxide possessing a 200,000 molecular weight, 12% poloxamer 407 (LUTROL F127), 3% polyvinylpyrrolidone possessing a 40,000 molecular weight, 0.1% ferric oxide and 1% stearic acid. The push layer was comprised of 64.3% polyethylene

oxide comprising a 7,000,000 molecular weight, 30% sodium chloride, 5% polyvinylpyrrolidone possessing an average molecular weight of 40,000, 0.4% ferric oxide, 0.05% butylated hydroxytoluene (BHT), and 0.25% stearic acid. The bi-layer membrane laminate in which the first membrane layer was comprised of 55% ethylcellulose, 45% hydroxylpropyl cellulose and 5% POLYOXYL 40 stearate (PEG 40 stearate or MYRJ 52S), and the second membrane laminate was a semi-permeable wall which was comprised of 80% cellulose acetate of 39.8% acetyl content and 20% poloxamer 188 (PLURONIC F68 or LUTROL F68). The dosage form comprised one passageway, 30 mils (0.76 mm) on the center of the drug side. The final dosage form could contained a color overcoat and a clear overcoat.

**[000340]** The final dosage form release topiramate such that about 90% of the drug was release with a substantially ascending rate of release over approximately 16 hours, as shown in Figure 11.

### **Example 8**

#### **Topiramate Capsule Shaped Bi-layer 100 mg System**

**[000341]** A dosage form was manufactured as follows. First, 2880 g of topiramate, 958 g of polyethylene oxide with average molecular weight of 200,000 and 4980 g of poloxamer 407 (LUTROL F127) having an average molecular weight of 12,000 were added to a fluid bed granulator bowl. Next two separate binder solutions, a poloxamer binder solution and a polyvinylpyrrolidone identified as K29-32 having an average molecular weight of 40,000 binder solution were prepared by dissolving 500 g of the same poloxamer 407 (LUTROL F127) in 4500 g of water and 750 g of the same polyvinylpyrrolidone in 4250 of water, respectively. The dry materials were fluid bed granulated by first spraying with 3780 g of the poloxamer binder solution and followed by spraying 3333 g of the polyvinylpyrrolidone binder solution. Next, the wet granulation was dried in the granulator to an acceptable moisture content, 0.5%, and sized using by passing through a 7-mesh screen. Next, the granulation was transferred to a blender and mixed with 2 g of butylated hydroxytoluene (BHT) as an antioxidant and lubricated with 200 g of stearic acid and 100 g of magnesium stearate.

**[000342]** Next, a push layer was prepared as follows. First, a binder solution was prepared. 7.5 kg of polyvinylpyrrolidone identified as K29-32 having an average molecular weight of 40,000 was dissolved in 50.2 kg of water. Then, 37.5 kg of sodium chloride and 0.5 kg of ferric oxide were sized using a Quadro Comil with a 21-mesh screen. Then, the screened materials and 80.4 kg of polyethylene oxide (approximately 7,000,000 molecular weight) were added to a fluid bed granulator bowl. The dry materials were fluidized and mixed while 48.1 kg of binder solution was sprayed from 3 nozzles onto the powder. The granulation was dried in the fluid-bed chamber to an acceptable moisture level. The coated granules were sized using a Fluid Air mill with a 7-mesh screen. The granulation was transferred to a tote tumbler, mixed with 63 g of butylated hydroxytoluene and lubricated with 310 g stearic acid.

**[000343]** Next, the drug composition and the push composition were compressed into bi-layer tablets on multilayer Korsch press. First, 278 mg of the drug composition was added to the die cavity and pre-compressed, then, the push composition was added to achieve the total system weight of 463 mg and the layers were pressed into a 15/64" diameter, capsule shaped, deep concave, bi-layer arrangement.

**[000344]** The bi-layer arrangements were coated with bi-layer polymer membrane laminate in which the first coating layer was a rigid yet water permeable laminate and the second coating layer was a semi-permeable membrane laminate. The first membrane laminate composition comprised 55% ethylcellulose, 45% hydroxylpropyl cellulose and 5% POLYOXYL 40 stearate (PEG 40 stearate or MYRJ 52S). The membrane-forming composition was dissolved in 100% ethyl alcohol to make a 7% solids solution. The membrane-forming composition was sprayed onto and around the arrangements in a pan coater until approximately 38 mg of membrane was applied to each tablet.

**[000345]** Next, the bi-layer arrangements coated with the first membrane laminate were coated with the semi-permeable membrane. The membrane forming composition comprised 80% cellulose acetate having a 39.8% acetyl content and 20% poloxamer 188 (PLURONIC F68 or LUTROL F68). The membrane-forming composition was dissolved in 100% acetone solvent to

make a 5% solids solution. The membrane-forming composition was sprayed onto and around the arrangements in a pan coater until approximately 30 mg of membrane was applied to each tablet.

5     **[000346]**     Next, one 45 mil (1.14 mm) exit passageway was laser drilled through the bi-layer membrane laminate to connect the drug layer with the exterior of the dosage system. The residual solvent was removed by drying for 72 hours at 40°C and ambient humidity.

10     **[000347]**     Next, the drilled and dried dosage forms were coated with an immediate release drug overcoat. The drug overcoat was a 13% solids aqueous solution containing 780 g of topiramate, 312 g of coPOVIDONE (KOLLIDONE VA 64) and 208 g of hydroxypropyl methycellulose possessing an average molecular weight of 11,200. The drug overcoat solution as sprayed onto the dried coated cores until an average wet coated weight of approximately 33 mg per system was achieved.

15     **[000348]**     Next, the drug-over coated systems were color over coated. The color overcoat was a 12% solids suspension of OPADRY in water. The color overcoat suspension was sprayed onto the drug over coated systems until an average wet coated weight of approximately 25 mg per system was achieved.

20     **[000349]**     Next, the color-over coated systems were clear coated. The clear coat was a 5% solids solution of OPADRY in water. The clear coat solution as sprayed onto the color coated cores until an average wet coated weight of approximately 25 mg per system was achieved.

25     **[000350]**     The dosage form produced by this manufacture was designed to deliver 20 mg of topiramate as an immediate release from an overcoat comprised of 60% topiramate, 24% co-POVIDONE and 16% hydroxypropyl methylcellulose followed by the controlled delivery of 80 mg of topiramate from the drug composition containing 28.8% topiramate, 9.58% polyethylene oxide possessing a 200,000 molecular weight, 53.6% poloxamer 407 (LUTROL F127), 5% polyvinylpyrrolidone possessing a 40,000 molecular weight, 0.02% butylated hydroxytoluene (BHT), 2% stearic acid and 1% magnesium Stearate.

30     The push layer was comprised 64.3% polyethylene oxide comprising a 7,000,000 molecular weight, 30% sodium chloride, 5% polyvinylpyrrolidone possessing an average molecular weight of 40,000, 0.4% ferric oxide, 0.05%

butylated hydroxytoluene, and 0.25% stearic acid. The bi-layer membrane laminate in which the first membrane layer was comprised of 55% ethylcellulose, 45% hydroxylpropyl cellulose and 5% POLYOXYL 40 stearate (PEG 40 stearate or MYRJ 52S), and the second membrane laminate is a semi-permeable wall which was comprised of 80% cellulose acetate of 39.8% acetyl content and 20% poloxamer 188 (PLURONIC F68 or LUTROL F68). The dosage form comprised one passageway, 45 mils (1.14 mm) on the center of the drug side. The final dosage form contained a color overcoat and a clear overcoat.

10 **[000351]** The final dosage form had a mean release rate of 6 mg topiramate per hour releasing the topiramate with a substantially zero-order rate or release, as shown in Figure 12.

#### **Examples 9-14**

#### 15 **Topiramate Dosage Forms**

**[000352]** Tables 1-9 below list composition details for additional embodiments of the present invention. More particularly, the tables below provide details on the composition of tri-layer, controlled release, osmotic dosage forms containing topiramate. Said dosage forms comprised two drug compositions, wherein the amount and / or concentration of topiramate in the two drug compositions was different, and a push layer.

**[000353]** Each of the dosage forms described below was prepared according to the procedure described in Example 15, by selecting and substituting the suitable components.

25 **[000354]** Table 1 below lists the components of dosage forms as a function of total dosage of topiramate. For each layer or coating, weights are listed in milligrams (e.g for the drug layers, push layers, semi-permeable membranes, other coatings, etc.). Also listed in Table 1 are the sizes for each dosage form, as prepared.

30



**Table 1: Dosage Form Components**

Dosage	10 mg	20 mg	45 mg	90 mg	135 mg	180 mg
Size (inches)	3/16	15/64	3/16	15/64	17/64	9/32
Drug Layer 1	60	120	60	120	180	240
Drug Layer 2	60	120	60	120	180	240
Push Layer	90	180	90	180	270	360
Subcoat	15	20	15	20	25	25
Membrane Coat (99:1 CA:poloxamer)	32	40	36	40	46	50
Membrane Coat (78:22 CAB:poloxamer)	28	38	28	38	42	48

CA = cellulose acetate

CAB = cellulose acetate butyrate

- 5 **[000355]** Table 2 below lists the components and amounts used in the preparation of the first drug composition for dosage forms comprising 45-180 mg total of topiramate. Target % (wt/wt) in granulation is the weight percent of the component as a function of the total weight of the drug layer.

10

**Table 2: First Drug Composition (45-180 mg Dosages)**

Material ID	Target % (wt/wt) in Granulation
Topiramate	32.00
Polyethylene Oxide, NF, N-80, 200K, TG, LEO	16.23
POVIDONE, USP, Ph Eur, (K29-32)	3.00
Poloxamer 407, NF (Micronized)	42.00
Methylcellulose, USP, 15CPS, (A15-LV-PREMIUM)	2.50
Stearic Acid, NF, Ph Eur (Powder)	3.00
Magnesium Stearate, NF, Ph Eur	1.25
BHT, FCC, Ph Eur (Milled)	0.02

**[000356]** Table 3 below lists the components and amounts used in the preparation of the second drug composition for dosage forms comprising 45-180 mg total of topiramate. Target % (wt/wt) in granulation is the weight percent of the component as a function of the total weight of the drug layer.

**Table 3: Second Drug Composition (45-180 mg Dosages)**

<b>Material ID</b>	<b>Target % (wt/wt) in Granulation</b>
Topiramate	43.00
POVIDONE, USP, Ph Eur, (K29-32)	3.00
Poloxamer 407, NF (Micronized)	49.90
Methylcellulose, USP, 15CPS, (A15-LV-PREMIUM)	2.50
Ferric Oxide, NF, (Yellow)	0.08
Stearic Acid, NF, Ph Eur (Powder)	1.00
Magnesium Stearate, NF, Ph Eur	0.50
BHT, FCC, Ph Eur (Milled)	0.02

**[000357]** Table 4 below lists the components and amounts used in the preparation of the first drug composition for dosage forms comprising 10-20 mg total of topiramate. Target % (wt/wt) in granulation is the weight percent of the component as a function of the total weight of the drug layer.

**Table 4: First Drug Composition (10-20 mg doageses)**

<b>Material ID</b>	<b>Target % (wt/wt) in Granulation</b>
Topiramate	5.00
Polyethylene Oxide, NF, N-80, 200K, TG, LEO	88.73
Poloxamer 407, NF (Micronized)	2.00
POVIDONE, USP, Ph Eur, (K29-32)	3.00
Stearic Acid, NF, Ph Eur (Powder)	1.00
Magnesium Stearate, NF, Ph Eur	0.25

BHT, FCC, Ph Eur (Milled)	0.02
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[000358] Table 5 below lists the components and amounts used in the preparation of the second drug composition for dosage forms comprising 10-20 mg total of topiramate. Target % (wt/wt) in granulation is the weight percent of the component as a function of the total weight of the drug layer.

**Table 5: Second Drug Composition (10-20 mg Dosages)**

Material ID	Target % (wt/wt) in Granulation
Topiramate	12.00
Polyethylene Oxide, NF, N-80, 200K, TG, LEO	71.72
Poloxamer 407, NF (Micronized)	12.00
POVIDONE, USP, Ph Eur, (K29-32)	3.00
Iron Oxide, Red	0.01
Stearic Acid, NF, Ph Eur (Powder)	1.00
Magnesium Stearate, NF, Ph Eur	0.25
BHT, FCC, Ph Eur (Milled)	0.02

[000359] Table 6 below lists the components and amounts used in the preparation of the push layer for all dosage forms of topiramate. Target % (wt/wt) in granulation is the weight percent of the component as a function of the total weight of the drug layer.

**Table 6: Push Layer Composition**

Material ID	Target % (wt/wt) in Granulation
Polyethylene Oxide, NF, 303, 7000K, TG, LEO	64.3
Sodium Chloride, USP, Ph Eur, (Powder)	30.0
POVIDONE, USP, Ph Eur, (K29-32)	5.0
Ferric Oxide, NF, (Red)	0.1
Ferric Oxide, NF, (Yellow)	0.3
Stearic Acid, NF, Ph Eur, (Powder)	0.25

BHT, FCC, Ph Eur, (Milled)	0.05
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**[000360]** Table 7 below lists the components and amounts used in the preparation of the subcoat (aqueous subcoat) for all dosage forms of topiramate. Target % (wt/wt) in subcoat formulation is the weight percent of the component as a function of the total weight of the subcoat.

**Table 7: Subcoat Composition**

Material ID	Target % (wt/wt) in Subcoat Formulation
Hydroxyethyl Cellulose, NF	95
Polyethylene Glycol 3350, NF, Ph Eur, LEO	5

**[000361]** Tables 8 and 9 below list the components and amounts used in the preparation of the CAB (cellulose acetate butyrate) membrane coat and the CA (cellulose acetate) membrane coat, respectively, for all dosage forms of topiramate. Target % (wt/wt) in subcoat formulation is the weight percent of the component as a function of the total weight of the subcoat.

**Table 8: CAB Membrane Coat**

Material ID	Target % (wt/wt) in Subcoat Formulation
Cellulose Acetate Butyrate (171-15)	78
Poloxamer 188, NF, Ph Eur	22

**Table 9: CA Membrane Coat**

Material ID	Target % (wt/wt) in Subcoat Formulation
Cellulose Acetate, NF, (398-10)	99
Poloxamer 188, NF, Ph Eur	1

### **Example 15**

#### **Large Scale Manufacture of Topiramate Dosage Forms**

5 [000362] A push layer granulation was manufactured as follows. The composition of the push layer was as follows: 64.3% polyethylene oxide, 30% sodium chloride, 5% POVIDONE, 0.4% ferric oxide, 0.25% stearic acid and 0.05% butylated hydroxytoluene.

10 [000363] A binder solution was prepared as follows: 7.5 kg of POVIDONE was added to 50.2 kg of purified water in a mixing vessel and mixed until the POVIDONE was completely in solution. The net weight of the prepared binder solution was determined by weighing.

15 [000364] The dry ingredients – 80.4 kg of polyethylene oxide, 37.5 kg of sodium chloride and 0.5 kg of ferric oxide were charged into a tote. The fluid bed granulator was assembled with the guns required for spraying the binder solution. The granulator was then warmed to an inlet air temperature of 43-47°C and 48 kg of the binder solution was metered into the granulator. After the spraying was completed, the granules were allowed to dry in the granulator until a moisture content less than or equal to 1% was obtained. The dried granules were then milled through a Granumill using a 7 mesh screen. The milled granulation was weighed and collected in a tote. 0.05% butylated hydroxytoluene by weight of the granulation was added to the tote and the granulation was mixed for 5 min. Stearic acid amount equivalent to 0.25% of the granulation was weighed and added to the tote. The granules were then mixed for an additional 5 minutes.

25 [000365] A granulation for the first drug composition was manufactured as follows. The composition of the first drug composition was as follows: 32% topiramate, 16.23% polyethylene oxide, 42% poloxamer 407, 3% POVIDONE, 2.5% methyl cellulose, 3% stearic acid, 1.25% magnesium stearate and 0.02% butylated hydroxytoluene.

30 [000366] A binder solution was prepared as follows: 480 g of POVIDONE was added to 4.32 kg of purified water in a mixing vessel and mixed until the POVIDONE was completely in solution. The net weight of the prepared binder solution was determined by weighing.



**[000367]** A methyl cellulose granule coating solution was prepared as follows: 2.6 kg of purified water was heated to a temperature greater than 50°C. 400 g of methylcellulose is gradually added to the hot water while mixing. Mixing was continued until all solids were dispersed. 5 kg of purified water was then added to the mixing vessel and mixing was continued until all solids were dissolved. The net weight of prepared granule coating solution was determined by weighing.

**[000368]** The dry ingredients – 3.2 kg topiramate, 1.623 kg polyethylene oxide, and 4.2 kg poloxamer were charged into a tote. The fluid bed granulator was assembled with the guns required for spraying the binder solution. The granulator was then warmed to an exhaust air temperature less than 25°C and 3 kg of the binder solution was metered into the granulator. Following the spraying of the binder solution, 5 kg of granule coating solution was sprayed onto the granules. After spraying was completed, the granules were allowed to dry in the granulator until a moisture content less than or equal to 0.5% was obtained. The dried granulation was then milled through a Granumill using a 7 mesh screen. The milled granulation was weighed and collected in a tote. 0.05% butylated hydroxytoluene by weight of the granulation was added to the tote and the granulation was mixed for 5 min. Stearic acid amount equivalent to 3% of the granulation was weighed and added to the tote. The granules were then mixed for an additional 5 minutes. Magnesium stearate amount equivalent to 1.25% of the granulation was weighed and added to the tote. The granules were then mixed for an additional 30 seconds.

**[000369]** A granulation for the second drug composition was manufactured as follows. The composition of the second drug composition was as follows: 43% topiramate, 49.9% poloxamer 407, 3% POVIDONE, 2.5% methyl cellulose, 1% stearic acid, 0.5% magnesium stearate, 0.08% yellow ferric oxide, and 0.02% butylated hydroxytoluene.

**[000370]** A binder solution was prepared as follows: 480 g of POVIDONE was added to 4.32 kg of purified water in a mixing vessel and mixed until the POVIDONE was completely in solution. The net weight of the prepared binder solution was determined by weighing.

**[000371]** A methyl cellulose granule coating solution was prepared as follows: 2.6 kg of purified water was heated to a temperature greater than 50°C. 400 g of methylcellulose was gradually added to the hot water while mixing. Mixing was continued until all solids were dispersed. 5 kg of purified water was then added to the mixing vessel and mixing was continued until all solids are dissolved. The net weight of prepared granule coating solution was determined by weighing.

**[000372]** The dry ingredients – 4.3 kg Topiramate, 4.9 kg poloxamer and 8 g ferric oxide were charged into a tote. The fluid bed granulator was assembled with the guns required for spraying the binder solution. The granulator was then warmed to an exhaust air temperature less than 25°C and 3 kg of the binder solution was metered into the granulator. Following the spraying of the binder solution, 5 kg of granule coating solution was sprayed onto the granules. After spraying was completed, the granules were allowed to dry in the granulator until a moisture content less than or equal to 0.5% was obtained. The dried granulation was then milled through a Granumill using a 7 mesh screen. The milled granulation was weighed and collected in a tote. 0.05% butylated hydroxytoluene by weight of the granulation was added to the tote and the granulation was mixed for 5 min. Stearic acid amount equivalent to 1% of the granulation was weighed and added to the tote. The granules were then mixed for an additional 5 minutes. Magnesium stearate amount equivalent to 0.5% of the granulation was weighed and added to the tote. The granules were then mixed for an additional 30 seconds.

**[000373]** Compression of cores was completed as follows. The above granulations were compressed into a trilayer tablet core. Different weights were compressed into different size cores for the various doses.

**[000374]** A trilayer tablet core to deliver 90 mg drug was compressed as follows: 28.6% by weight of drug layer 1, 28.6% by weight of drug layer 2 and 42.9% by weight of push layer were compressed to form a trilayer tablet on a Korsch Tablet press. For the 90 mg tablet 120 mg drug layer 1, 120 mg drug layer 2 and 180 mg push layer were compressed together using a 15/64" diameter tooling set.

**[000375]** Subcoat application was completed as follows. The composition of the subcoat was as follows: 95% hydroxyethyl cellulose and 5% polyethylene glycol 3350.

5 **[000376]** A subcoating solution was prepared as follows: 14.1 kg of water was added to a mixing vessel. 45 g of polyethylene glycol was added and mixed until all solids were dissolved. 855 g of hydroxyethyl cellulose was weighed and charged to the PEG solution while mixing. Mixing was continued until all solids were dissolved. The net weight of the prepared subcoating solution was determined by weighing.

10 **[000377]** 9 kg of compressed cores was charged to a coater and the cores were tumbled in the coater until a target exhaust temperature of 32°C was achieved. The subcoating solution was applied to the cores while the coater was rotated at 12 rpm. Coating was continued until the target weight of 34 mg is achieved. At the end of the spray, the cores were removed from the coater.

15 **[000378]** The rate controlling membrane was completed as follows. The composition of the rate controlling membrane was as follows: 99% cellulose acetate and 1% poloxamer 188.

**[000379]** A membrane coating solution was prepared as follows: 47 kg of acetone was charged to a mixing vessel. The acetone was heated to 28°C  
20 while the mixer was turned on. 25 g of poloxamer was added to the acetone and mixed until completely dissolved. 2.475 kg of cellulose acetate was added to the poloxamer solution, followed by addition of 475 g of purified water. The solution was mixed until all solids are in solution. The net weight of the prepared membrane coating solution was determined by weighing.

25 **[000380]** 9 kg of subcoated cores were charged to a coater and the cores were tumbled in the coated until a target exhaust temperature of 32°C was achieved. The membrane coating solution was applied to the cores while the coater was rotated at 12 rpm. Coating was continued until the target weight of 36 mg was achieved. At the end of spray, the cores were removed from the  
30 coater.

**[000381]** The exit orifice was drilled and the dosage forms were then dried as follows. A 1mm orifice was drilled on the membrane coated cores using a

laser drilling device. The drilled cores were then spread out on drying trays and dried at 40°C at ambient humidity for up to 10 days.

### **Example 16**

#### **Topiramate Dosage Form**

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**[000382]** A drug core composition comprising 53.7 grams topiramate, 29.8 grams of CRODESTA F160, 10 grams of polyethylene oxide N-80 and 6 grams of polyethylene pyrrolidone K90, at less than 40 mesh particle sizes, were dry blended for approximately 30 minutes. The dry blend was then wetted with 20 grams of anhydrous ethyl alcohol SDA 3A while stirring to form a homogenous wet dough. The wet dough was passed thru #20 stainless steel screen to form noodles, and dried under a hood at ambient conditions for approximately 12 hours (overnight). The dried noodles were passed thru #20 stainless steel screen to form granules. These dried granules were then lubricated with 0.5 grams of <60 mesh magnesium stearate by roller blending for 3 minutes.

15

**[000383]** The push layer granulation was manufactured using the same process wherein 73.7 grams of polyethylene oxide 303, 20 grams of sodium chloride, 5 grams of polyvinyl pyrrolidone K2932, 1 gram of ferric oxide and 0.05 gram of BHT were dry blended for 30 minutes. The dry blend was then wetted with 80 grams of anhydrous ethyl alcohol SDA 3A while stirring, to form a homogenous wet dough. The wet dough was then passed thru a #20 mesh stainless steel screen to form noodles. These noodles were dried for approximately 12 hours under a hood at ambient conditions. The dried noodles were then passed thru a #20 mesh stainless steel screen to form granules. These dried granules were then lubricated with 0.25 grams of stearic acid by roller blending for 3 minutes.

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**[000384]** Both the drug and push layers were used to form a bilayer core using a 3/16-inch diameter LCT tooling. Drug layer granulation weighing 182 mg was introduced into the die first and then after slight tamping, the push layer granulation weighing 60 mg were then introduced and then compressed with a Carver Press at 0.75 ton compression force. This procedure was repeated until a desired amount of test tablets were produced. For initial trials 10 tablets were produced.

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**[000385]** To these tablets, 3 layers of coating were applied. The first coating, a smoothing coating, provided a smooth surface for the succeeding rate-controlling membrane coatings. For the smoothing coating, 5 grams of poloxamer 407 were dissolved in 783 grams of de-ionized water by stirring.

5 Then 45 grams of hydroxyethyl cellulose were introduced into the solution and stirred until a clear solution was achieved. An Aeromatic Coater was utilized for this coating. The 10 active tablets were mixed with placebo tablets (fillers) to provide a coater load of 500 grams. Standard Aeromatic Coating procedures were followed to coat approximately 3 to 4 mg of coating on each

10 active tablet. The coated active tablets were dried in an oven at 40°C and ambient humidity for approximately 12 hours.

**[000386]** The second coating was prepared by dissolving 77 grams of ethylcellulose (100cps), 56 grams of hydroxypropyl cellulose EFX, and 7 grams of MYRJ 52S in 4,527 grams of warm ethanol SDA3A while stirring. Stirring

15 was performed until a homogeneous solution was achieved. After stirring, the solution was sealed and stored at ambient conditions for approximately 2 days before application. An LDCS Vector Pan Coater was used for this coating. To achieve a 1.2 kg coater load, the 10 smooth coated active tablets were mixed with placebo filler tablets and coated with the second coating. Standard pan

20 coating procedures were used for the coating process with a target coat of approximately 6 mils.

**[000387]** For the third coating, 87.5 grams of cellulose acetate 398-10 and 37.5 grams of LUTROL F68 were dissolved in 2,375 grams acetone with stirring and warming. This coating was applied using the same coater and

25 standard coating procedure as with the second coat. After coating the active tablets were manually drilled to produce a 40 mil orifice, and then dried in an oven at 40°C and ambient humidity for approximately 12 hours (overnight).

**[000388]** Drug release rates and residuals were determined as described in Example 1 from 5 of these tablets at intervals of 2 hours for 24 hours. The

30 results, shown in Figure 14, show that topiramate was delivered at a substantially ascending rate of release for 12-14 hours. The time to deliver 90% of the 100 mg dose was approximately 16 hours. The cumulative delivery



at 24 hours was 99%. The membranes were intact throughout the delivery pattern.

### **Example 17**

#### **Topiramate Dosage Form**

5 [000389] Using the same granulation procedure described in Example 16, above, the following formulation consisting of 50 grams topiramate, 33.5 grams CRODESTA F-160, 10 grams polyethylene oxide N-80, and 6 grams of polyvinyl pyrrolidone K90, was wet granulated and lubricated with 0.5 gram and  
10 magnesium stearate. This constituted the drug layer with a load of 33.5 % surfactant. Tablets were made following the procedures and materials described in Example 16.

[000390] Drug release rates were determined as described in Example 1. The results, shown in Figure 15, show that topiramate was delivered at a  
15 substantially ascending rate of release for 12-14 hours. The time to deliver 90% of the 100 mg dose was approximately 16 hours. The cumulative delivery at 24 hours was 99.5%. The membranes were intact throughout the delivery pattern.

### **Example 18**

#### **Topiramate Dosage Form**

[000391] Tablets were made as described in Examples 16 and 17, but using a drug layer granulation consisting of 38.5 % surfactant (CRODESTA F160). A push layer composition in the amount of 60 mg was used.  
25 Membrane compositions and amounts applied were approximately the same as counterpart tablets in Examples 16 and 17.

[000392] Drug release rates were determined on these tablets according to same procedures described in Example 1. The results, shown in Figure 16, show that topiramate was delivered at a substantially ascending rate of release  
30 for 14-16 hours. The time to deliver 90% of the 100 mg dose was approximately 17 hours. The cumulative delivery at 24 hours was 98.7%. The membranes were intact throughout the delivery pattern.

**Example 19****Topiramate Dosage Form**

[000393] Using standard procedures for fluid bed granulation, 288 grams of topiramate, 536 grams of CRODESTA F-160, 95.8 grams of polyethylene oxide N-80, and 5 grams of polyvinyl pyrrolidone were granulated. This granulation was then lubricated with 2 grams of stearic acid and 1 gram of magnesium stearate. A Glatt Fluid Bed Granulator (1 kg) capacity was utilized for this granulation.

[000394] To test if this granulation does or does not smear under manufacturing conditions, a tableting run was performed with a multi-layer tablet press (Korsch Multi-Layer Tablet Press). Using the same tablet press and parameters, another tableting run was performed using a counterpart granulation that contains poloxamer 407 as surfactant. It was observed that no smearing on the turret table and on the punches was observed with the granulation containing CRODESTA F160. In contrast, smearing was observed with the granulation containing poloxamer 407.

[000395] Therefore, the sugar ester surfactant provides an advantage in formulating dosage forms with respect to the poloxamer surfactant, and the sugar ester surfactant CRODESTA is another preferred surfactant for topiramate in the present invention.

**Examples 20-25****Topiramate Dosage Forms**

[000396] Tables 10-17 below list composition details for additional embodiments of the present invention. More particularly, the tables below provide details on the composition of tri-layer, controlled release, osmotic dosage forms containing topiramate. Said dosage forms comprised two drug compositions, wherein the amount and / or concentration of topiramate in the two drug compositions was different, and a push layer.

[000397] Each of the dosage forms described below was prepared according to the procedure described in Example 15, by selecting and substituting the suitable components.

- [000398]** Table 10 below lists the components of dosage forms as a function of total dosage of topiramate. For each layer or coating, weights are listed in milligrams (e.g for the drug layers, push layers, semi-permeable membranes, other coatings, etc.). Also listed in Table 1 are the sizes for each dosage form, and the orifice sizes on the dosage form, as prepared.

**Table 10: Dosage Form Components**

<b>Dosage</b>	<b>10 mg</b>	<b>20 mg</b>	<b>40 mg</b>	<b>80 mg</b>	<b>120 mg</b>	<b>160 mg</b>
Size (inches)	3/16	15/64	3/16	15/64	17/64	9/32
Drug Layer 1	40	80	60	120	180	240
Drug Layer 2	60	120	60	120	180	240
Push Layer	90	150	100	180	270	330
Subcoat (Aqueous)	15	20	15	20	25	25
Membrane Coat (99/1 CA/Poloxamer)	32	32	36	38		44
Orifice Size (mil)	1x40	1x40	1x40	1x40	2x60	2x80

CA = Cellulose Acetate

- [000399]** Table 11 below lists the components and amounts used in the preparation of the first drug composition for dosage forms comprising 40-160 mg total of topiramate. Target % (wt/wt) in granulation is the weight percent of the component as a function of the total weight of the drug layer.

**Table 11: First Drug Composition (40-160 mg Dosages)**

<b>Material ID</b>	<b>Target % (wt/wt) in Granulation</b>
Topiramate	29.67
Polyethylene Oxide, NF, N-80, 200K, TG, LEO	33.06
Povidone, USP, Ph Eur, (K29-32)	2.00
Poloxamer 407, NF (Micronized)	29.00
METHYLCELLULOSE, USP, 15CPS, (A15-LV-PREMIUM)	3.00
Stearic Acid, NF, Ph Eur (Powder)	3.00

Magnesium Stearate, NF, Ph Eur	0.25
BHT, FCC, Ph Eur (Milled)	0.02

**[000400]** Table 12 below lists the components and amounts used in the preparation of the second drug composition for dosage forms comprising 45-180 mg total of topiramate. Target % (wt/wt) in granulation is the weight percent of the component as a function of the total weight of the drug layer.

**Table 12: Second Drug Composition (40-160 mg Dosages)**

Material ID	Target % (wt/wt) in Granulation
Topiramate	37.00
Povidone, USP, Ph Eur, (K29-32)	2.00
Poloxamer 407, NF (Micronized)	54.65
METHYLCELLULOSE, USP, 15CPS, (A15-LV-PREMIUM)	3.00
Ferric Oxide, NF, (Yellow)	0.08
Stearic Acid, NF, Ph Eur (Powder)	3.00
Magnesium Stearate, NF, Ph Eur	0.25
BHT, FCC, Ph Eur (Milled)	0.02

**[000401]** Table 13 below lists the components and amounts used in the preparation of the first drug composition for dosage forms comprising 10-20 mg total of topiramate. Target % (wt/wt) in granulation is the weight percent of the component as a function of the total weight of the drug layer.

**Table 13: First Drug Composition (10-20 mg dosages)**

Material ID	Target % (wt/wt) in Granulation
Topiramate	6.25
Polyethylene Oxide, NF, N-80, 200K, TG, LEO	80.48
Poloxamer 407, NF (Micronized)	10.00

Povidone, USP, Ph Eur, (K29-32)	2.00
Stearic Acid, NF, Ph Eur (Powder)	1.00
Magnesium Stearate, NF, Ph Eur	0.25
BHT, FCC, Ph Eur (Milled)	0.02

[000402] Table 14 below lists the components and amounts used in the preparation of the second drug composition for dosage forms comprising 10-20 mg total of topiramate. Target % (wt/wt) in granulation is the weight percent of the component as a function of the total weight of the drug layer.

**Table 14: Second Drug Composition (10-20 mg Dosages)**

Material ID	Target % (wt/wt) in Granulation
Topiramate	12.50
Polyethylene Oxide, NF, N-80, 200K, TG, LEO	69.22
Poloxamer 407, NF (Micronized)	15.00
Povidone, USP, Ph Eur, (K29-32)	2.00
Iron Oxide, Red	0.01
Stearic Acid, NF, Ph Eur (Powder)	1.00
Magnesium Stearate, NF, Ph Eur	0.25
BHT, FCC, Ph Eur (Milled)	0.02

[000403] Table 15 below lists the components and amounts used in the preparation of the push layer for all dosage forms of topiramate. Target % (wt/wt) in granulation is the weight percent of the component as a function of the total weight of the drug layer.

**Table 15: Push Layer Composition**

Material ID	Target % (wt/wt) in Granulation
Polyethylene Oxide, NF, 303, 7000K, TG, LEO	74.30
Sodium Chloride, USP, Ph Eur, (Powder)	20.00
Povidone, USP, Ph Eur, (K29-32)	5.00



Ferric Oxide, NF, (Red)	0.10
Ferric Oxide, NF, (Yellow)	0.30
Stearic Acid, NF, Ph Eur, (Powder)	0.25
BHT, FCC, Ph Eur, (Milled)	0.05

5 **[000404]** Table 16 below lists the components and amounts used in the preparation of the subcoat (aqueous subcoat) for all dosage forms of topiramate. Target % (wt/wt) in subcoat formulation is the weight percent of the component as a function of the total weight of the subcoat.

**Table 16: Subcoat Composition**

Material ID	Target % (wt/wt) in Subcoat Formulation
Hydroxyethyl Cellulose, NF	95
Polyethylene Glycol 3350, NF, Ph Eur, LEO	5

10 **[000405]** Tables 17 below lists the components and amounts used in the preparation of the CA (cellulose acetate) membrane coat, for all dosage forms of topiramate. Target % (wt/wt) in subcoat formulation is the weight percent of the component as a function of the total weight of the subcoat.

**Table 17: CA Membrane Coat**

Material ID	Target % (wt/wt) in Subcoat Formulation
Cellulose Acetate, NF, (398-10)	99
Poloxamer 188, NF, Ph Eur	1

15

**[000406]** In as much as the foregoing specification comprises disclosed embodiments, it is understood what variations and modifications may be made herein, in accordance with the principles disclosed, without departing from the invention.

20

**What is claimed is:**

1. A drug composition comprising a pharmaceutical agent and a solubilizing agent, wherein the pharmaceutical agent is selected from a low solubility pharmaceutical agent or a low dissolution rate pharmaceutical agent, and wherein the pharmaceutical agent comprises greater than 11% by weight of the drug composition.
2. The drug composition of claim 1, wherein the solubilizing agent is a surfactant.
3. The drug composition of claim 2, wherein the surfactant comprises greater than about 10% by weight of the drug composition.
4. The drug composition of claim 3, wherein the surfactant is selected from polyoxyl 40 stearate, polyoxyl 50 stearate, KOLLIDON 12PF, KOLLIDON 17PF, KOLLIDON 25/30, KOLLIDON K90, LUTROL F68, LUTROL F87, LUTROL F127, LUTROL F108, MYRJ 52S, MYRJ 53, MYRJ 59FL, PVP K2932, sorbitan monopalmitate, sorbitan monostearate, glycerol monostearate, polyoxyethylene stearate, sucrose cocoate, polyoxyethylene 40 sorbitol lanolin derivative, polyoxyethylene 75 sorbitol lanolin derivative, polyoxyethylene 6 sorbitol beeswax derivative, polyoxyethylene 20 sorbitol beeswax derivative, polyoxyethylene 20 sorbitol lanolin derivative, polyoxyethylene 50 sorbitol lanolin derivative, polyoxyethylene 23 lauryl ether, polyoxyethylene 23 lauryl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 2 cetyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 2 stearyl ether, polyoxyethylene 21 stearyl ether, polyoxyethylene 100 stearyl ether, polyoxyethylene 10 cetyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 20 cetyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 2 stearyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 10 stearyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 20 stearyl ether with butylated hydroxyanisole

and citric acid added as preservatives, polyoxyethylene 21 stearyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 20 oleyl ether with butylated hydroxyanisole and citric acid added as preservatives, polyoxyethylene 40 stearate, polyoxyethylene 50 stearate, polyoxyethylene 100 stearate, sorbitan monopalmitate, sorbitan monostearate, sorbitan tristearate, polyoxyethylene 4 sorbitan monostearate, polyoxyethylene 20 sorbitan tristearate, or mixtures thereof.

5. The drug composition of claim 4, wherein the surfactant is selected from LUTROL F127, polyoxyl 40 stearate or polyoxyl 50 stearate.

6. The drug composition of claim 2, further comprising a structural polymer.

7. The drug composition of claim 6, wherein the structural polymer comprises between about 5% and about 85% by weight of the drug composition

8. The drug composition of claim 7, wherein the structural polymer is selected from poly(ethylene oxide), poly(methylene oxide), poly(butylene oxide) and poly(hexylene oxide); poly(carboxymethylcellulose), poly(alkali carboxymethylcellulose), poly(sodium carboxymethylcellulose), poly(potassium carboxymethylcellulose) poly(calcium carboxymethylcellulose), poly(lithium carboxymethylcellulose), hydroxypropylcellulose, hydroxypropylethylcellulose, hydroxypropylmethylcellulose, hydroxypropylbutylcellulose, hydroxypropylpentylcellulose, poly(vinylpyrrolidone), a bioerodible structural polymer, maltodextrin, polyvinyl pyrrolidone, a polyvinylpyrrolidone vinyl acetate copolymer, lactose, glucose, raffinose, sucrose, mannitol, sorbitol, zylitol, or mixtures thereof.

9. The drug composition of claim 8, wherein the structural polymer is selected from MALTRIN M100, POLYOX N10 or POLYOX N80.

10. A dosage form comprising the drug composition of claim 3.

11. A dosage form comprising the drug composition of claim 3 and a push layer comprising an osmopolymer and an osmoagent.

5 12. A dosage form comprising a core comprising the drug composition of claim 3 and a push layer comprising an osmopolymer; a semi-permeable wall surrounding the core; and an exit orifice through the semi-permeable wall for releasing the drug composition from the dosage form over a prolonged period of time.

10

13. A dosage form comprising

(a) a core comprising a first drug composition, a second drug composition and a push layer comprising an osmopolymer;

(b) a semi-permeable wall surrounding the core; and

15 (c) an exit orifice through the semi-permeable wall for releasing the drug compositions from the dosage form over a prolonged period of time;

wherein the first drug composition comprises a first pharmaceutical agent and a first solubilizing agent, wherein the first pharmaceutical agent is selected from a low solubility pharmaceutical agent or a low dissolution rate pharmaceutical agent; and

20

wherein the second drug composition comprises a second pharmaceutical agent and a second solubilizing agent, wherein the second pharmaceutical agent is selected from a low solubility pharmaceutical agent or a low dissolution rate pharmaceutical agent, and wherein the pharmaceutical agent comprises greater than 11% by weight of the second drug composition.

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14. The dosage form of Claim 13, wherein the first pharmaceutical agent and the second pharmaceutical agent are the same and wherein the concentration of the first pharmaceutical agent in the first drug composition is less than the concentration of the second pharmaceutical agent in the second drug composition.

30

15. The dosage form of claim 13, which provides a substantially ascending rate of release.

5 16. The dosage form of claim 13, which provides a substantially ascending drug plasma concentration.

10 17. The drug composition of claim 3, wherein the low solubility pharmaceutical agent is characterized by a solubility of less than about 50 mg/ml.

18. The drug composition of claim 17, wherein the low solubility pharmaceutical agent is characterized by a solubility of less than about 10 mg/ml.

15 19. The drug composition of claim 3, wherein the low dissolution rate pharmaceutical agent is characterized by a dissolution rate between about 0 mg/min/cm<sup>2</sup> and about 20 mg/min/cm<sup>2</sup>.

20 20. The drug composition of claim 3, wherein the pharmaceutical agent is micronized.

21. The drug composition of claim 3, wherein the surfactant is micronized.



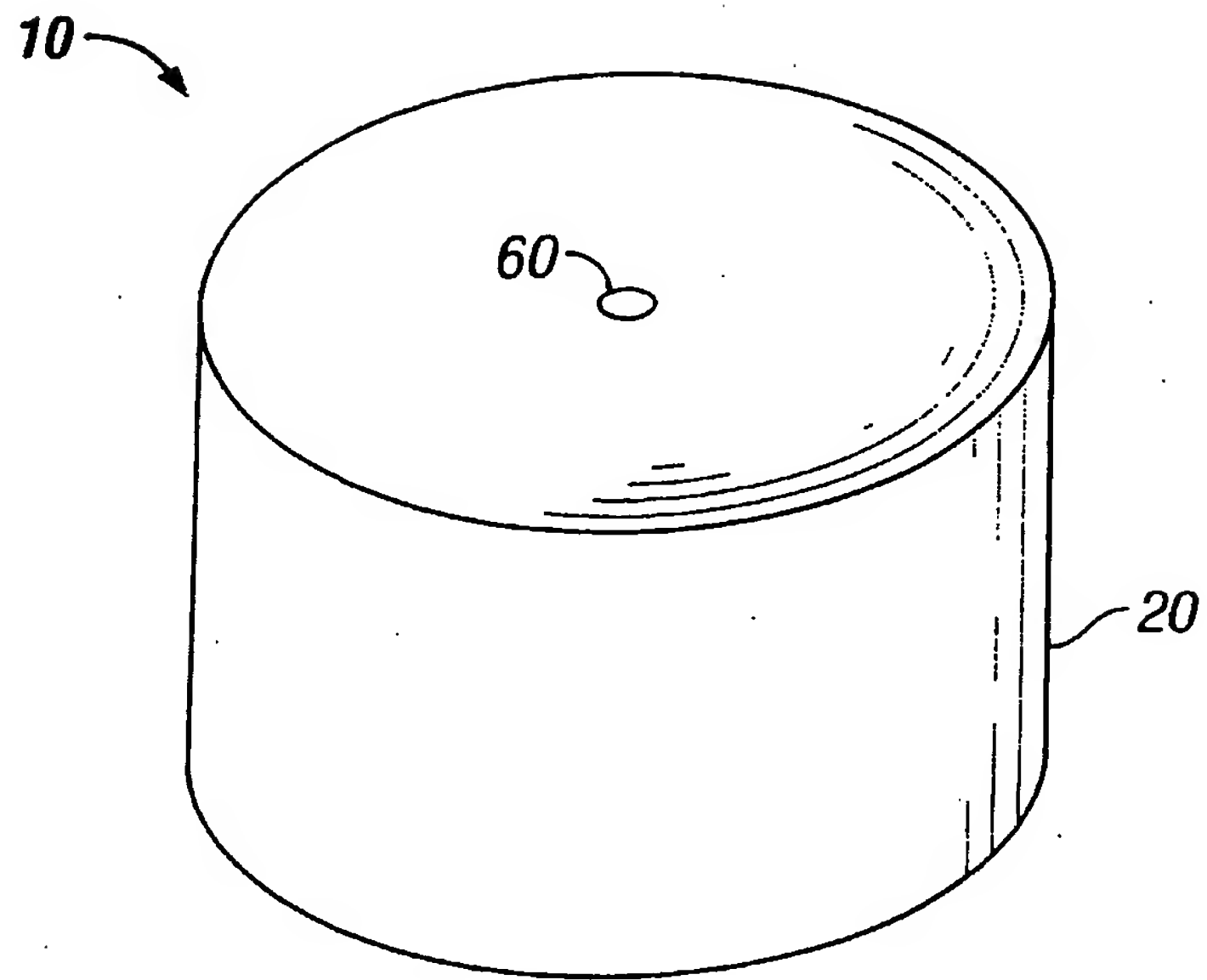


FIG. 1

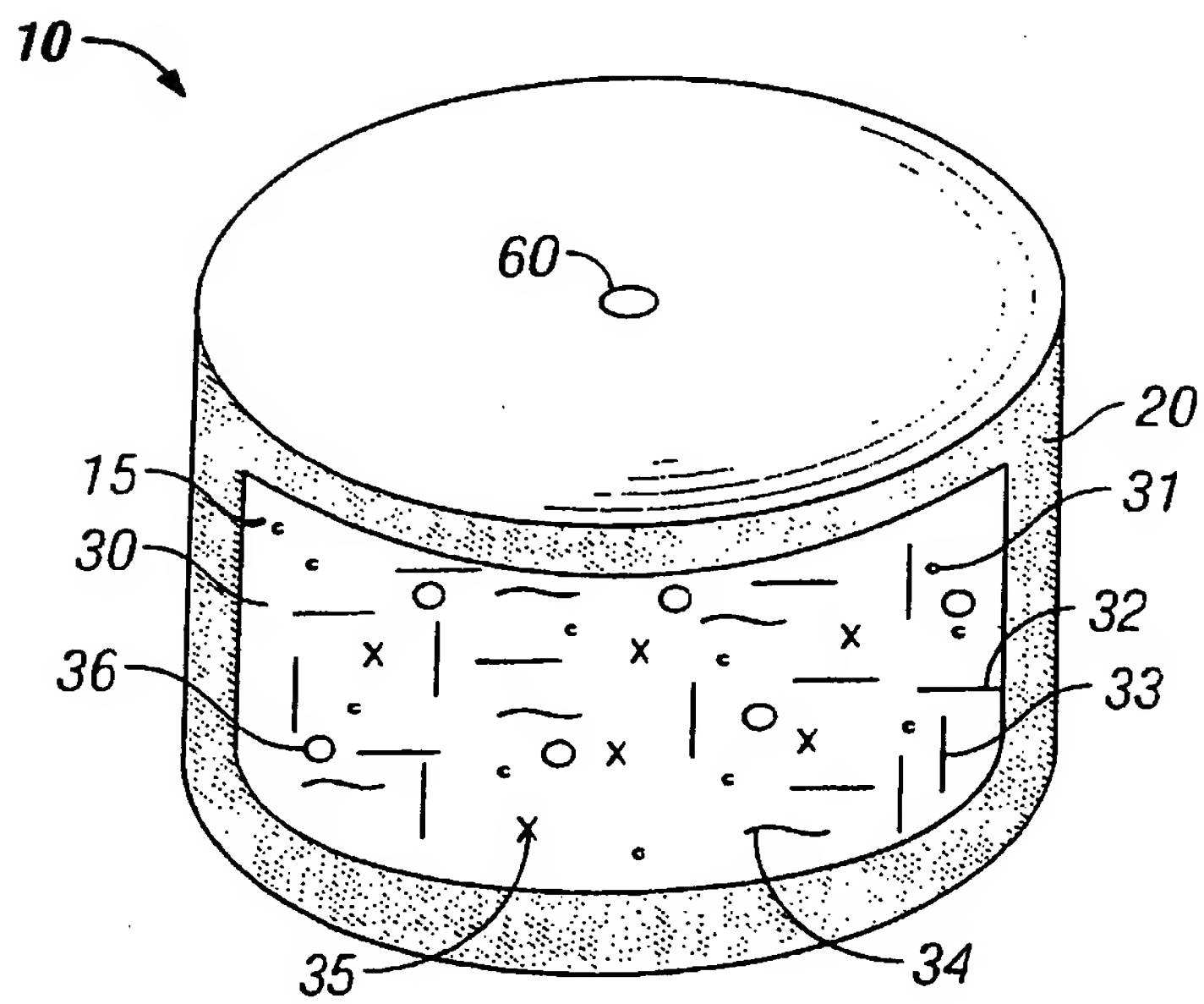


FIG. 2

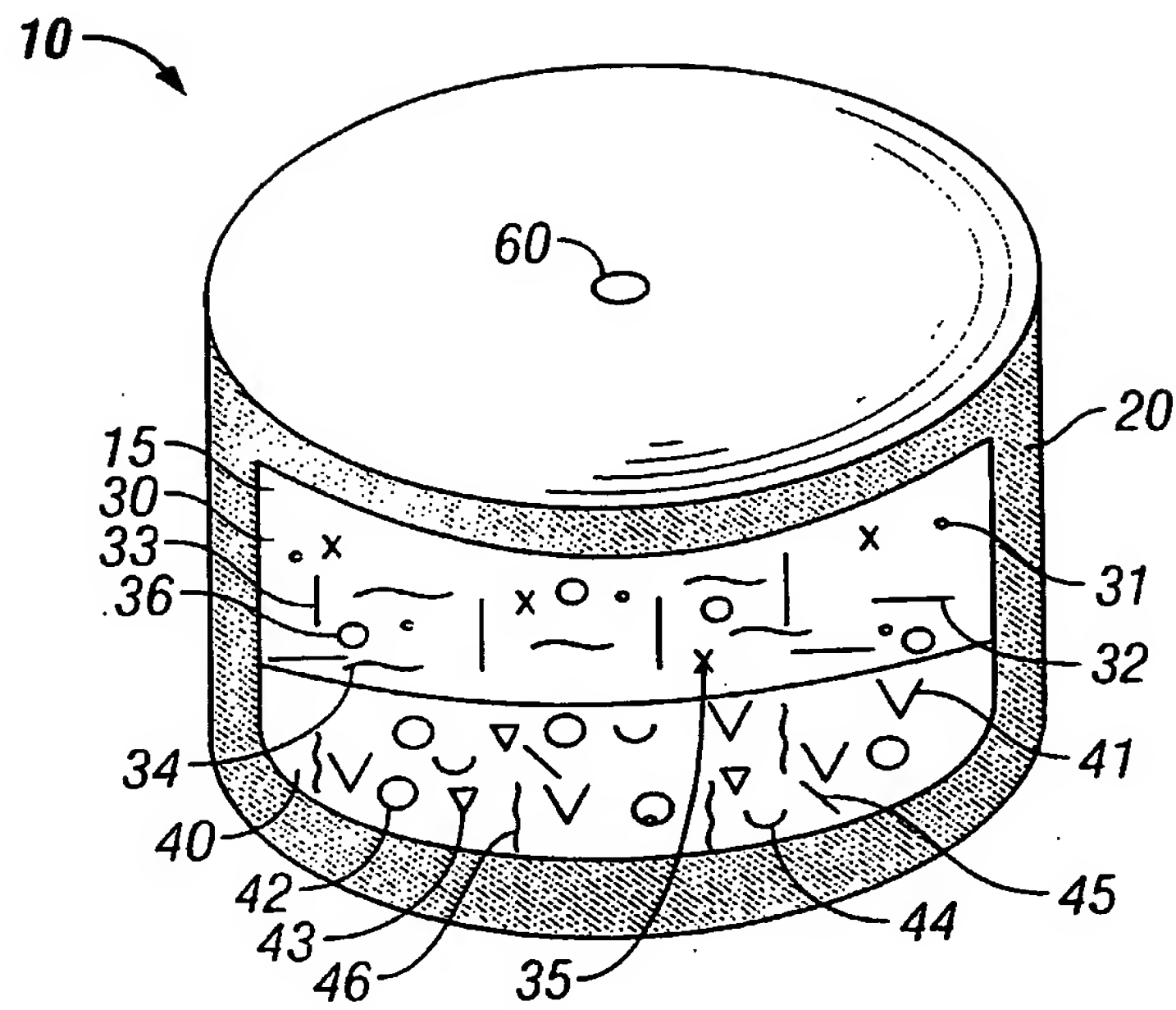


FIG. 3

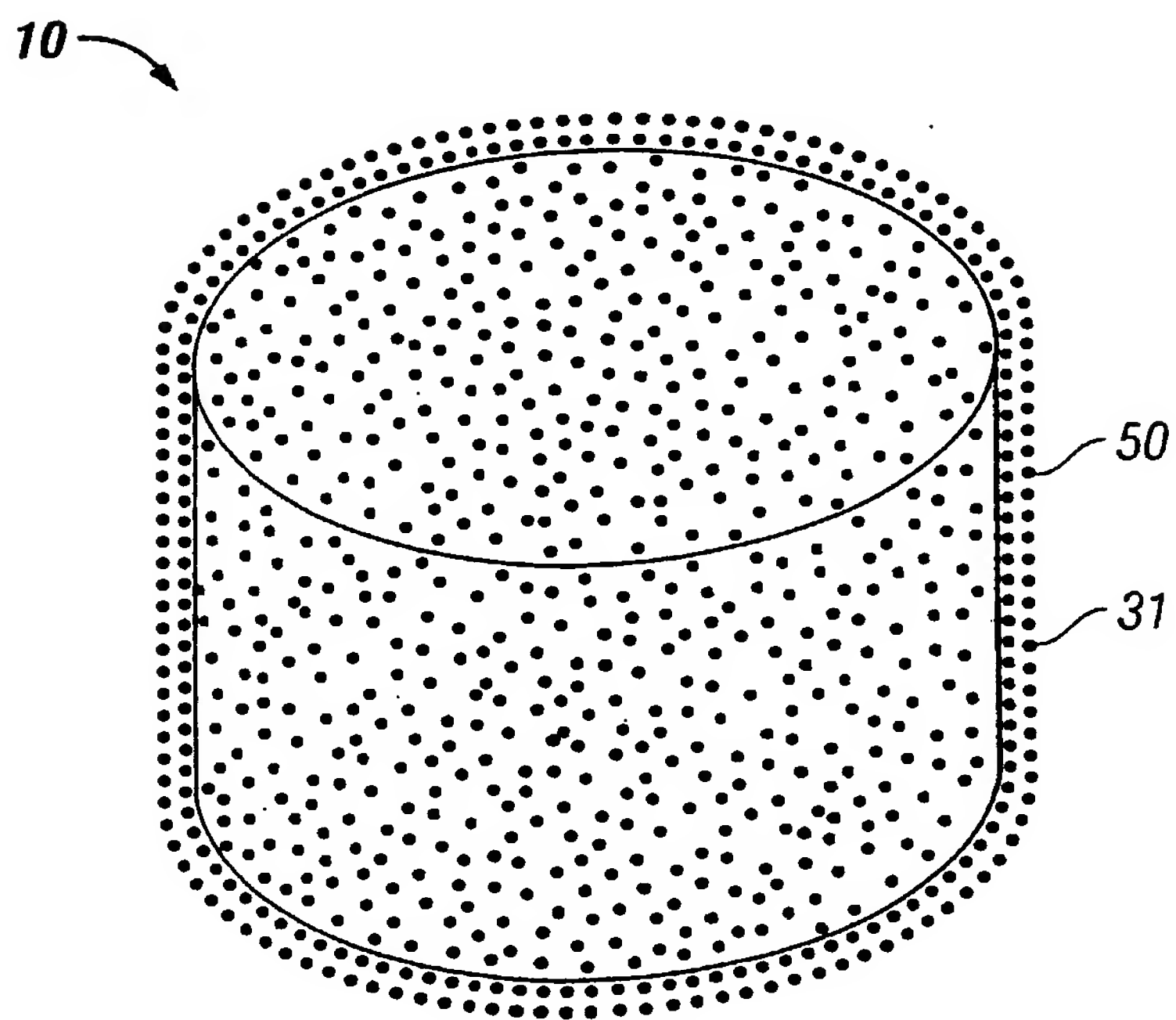


FIG. 4

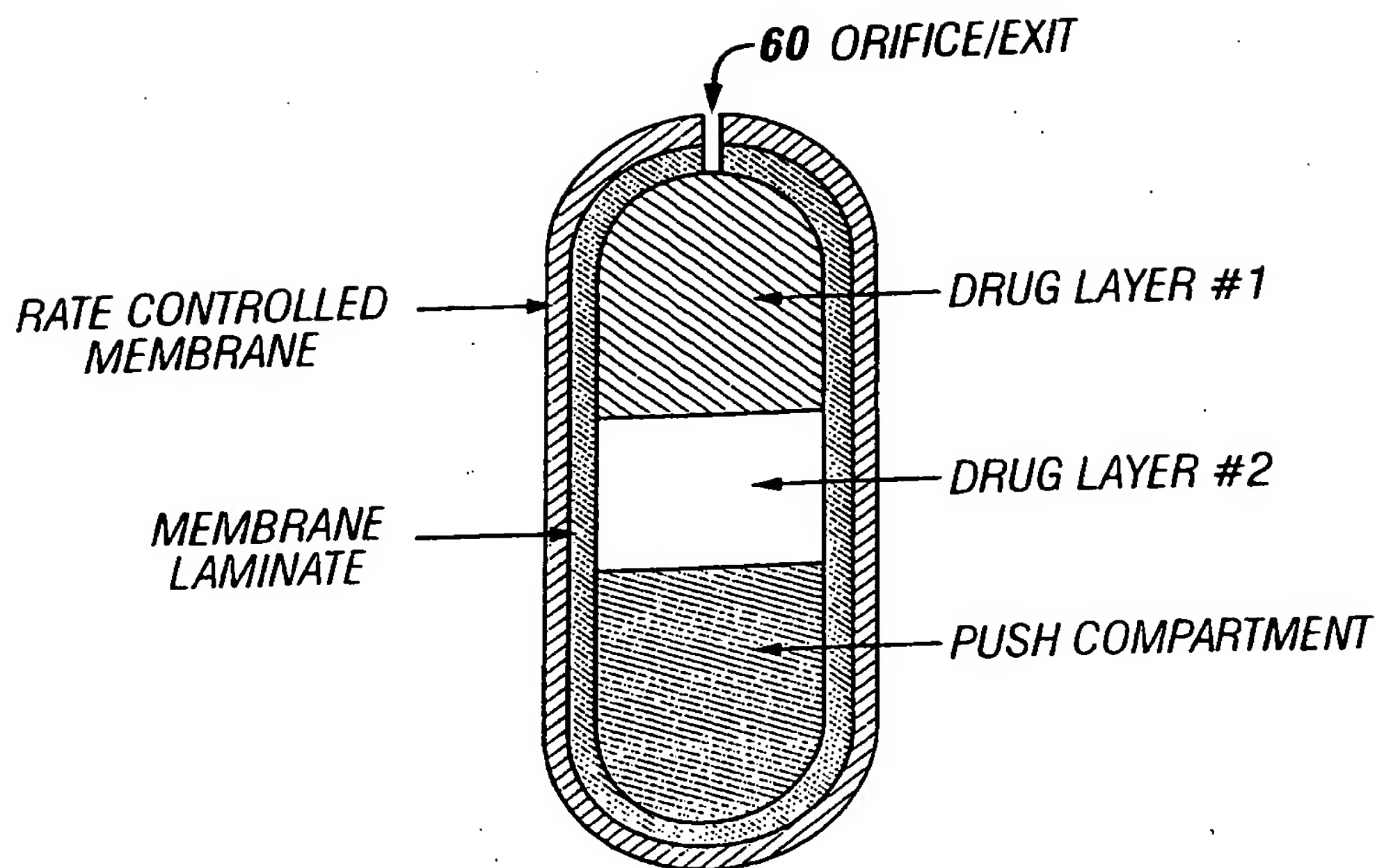


FIG. 5

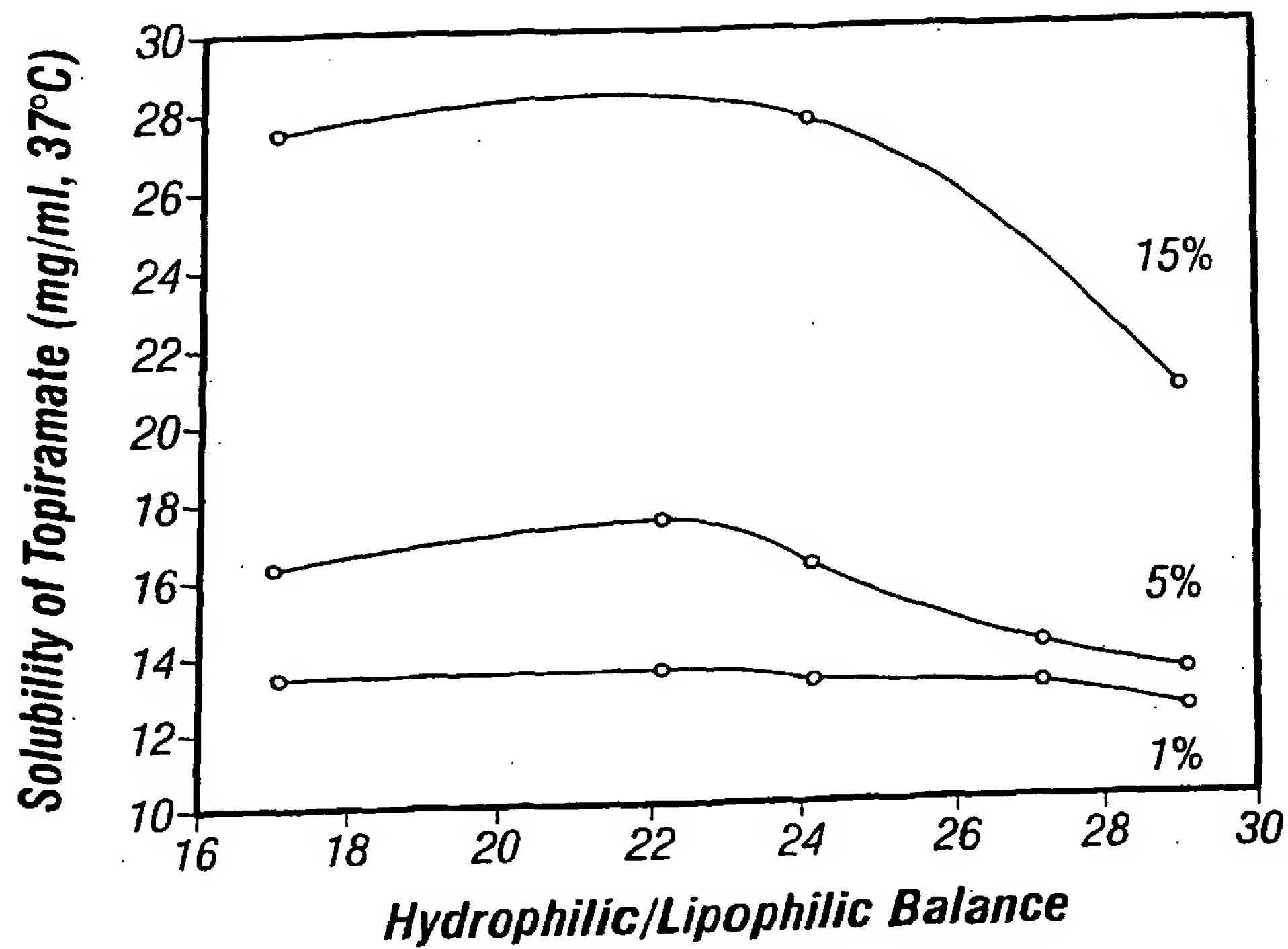


FIG. 6

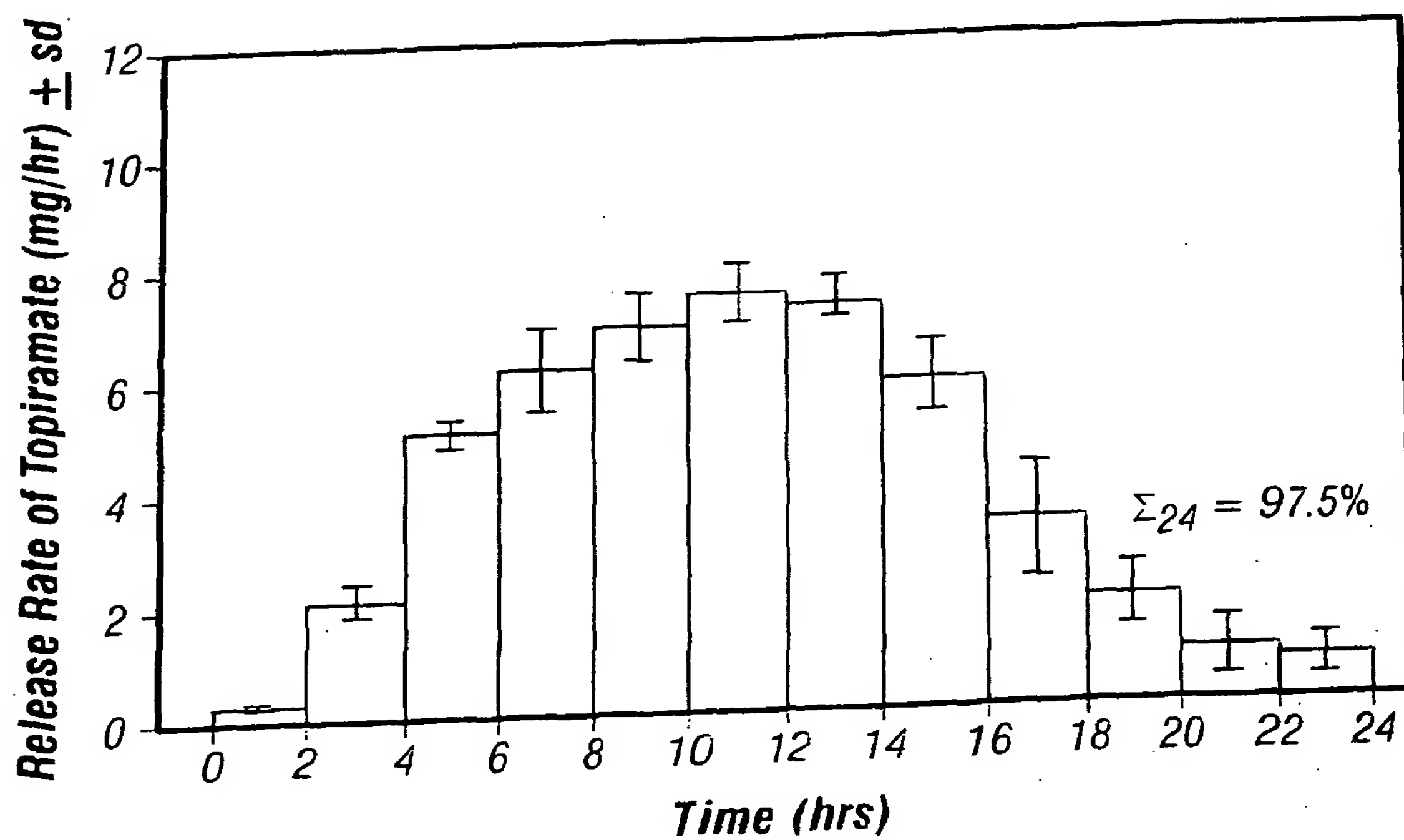


FIG. 7

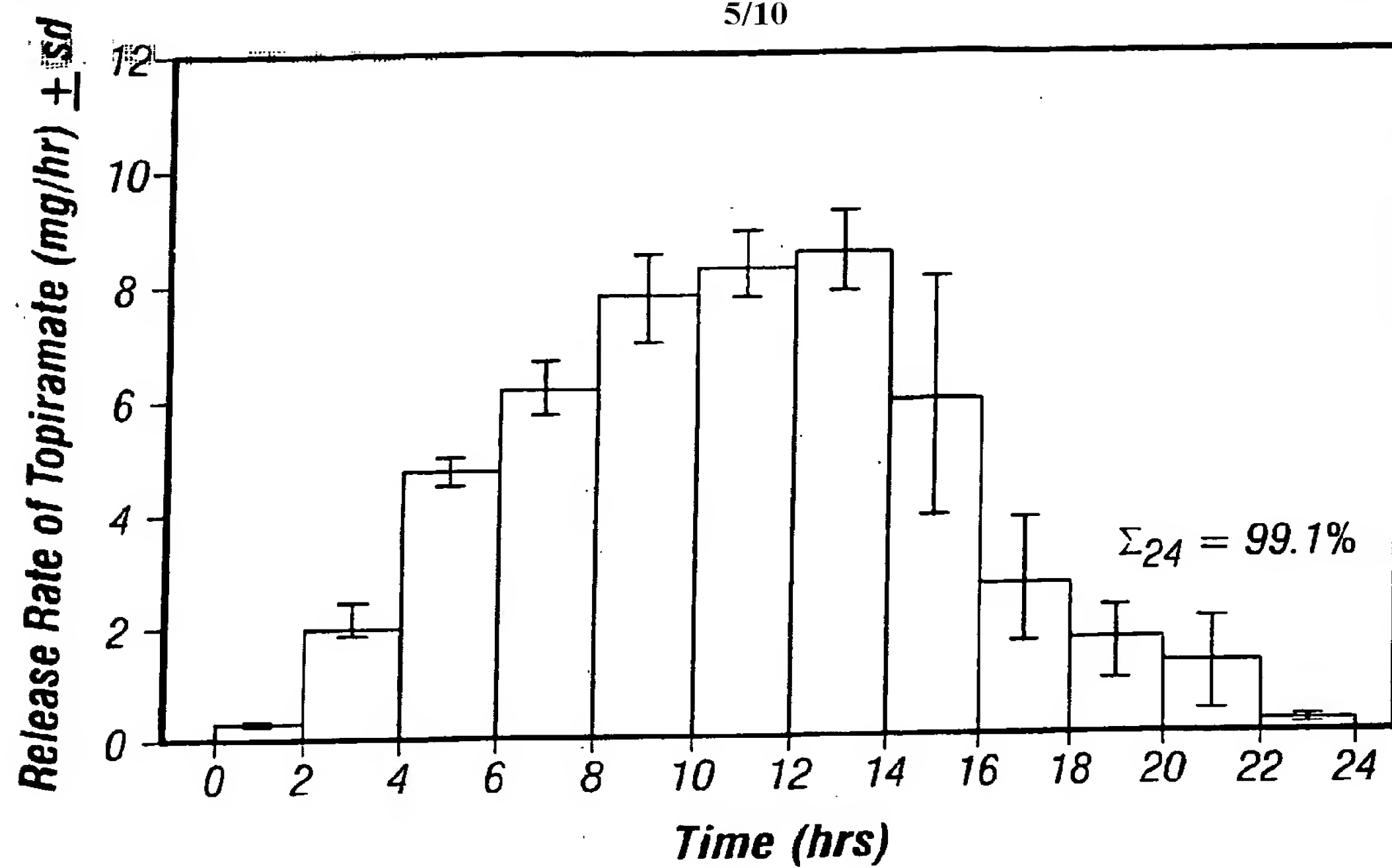


FIG. 8

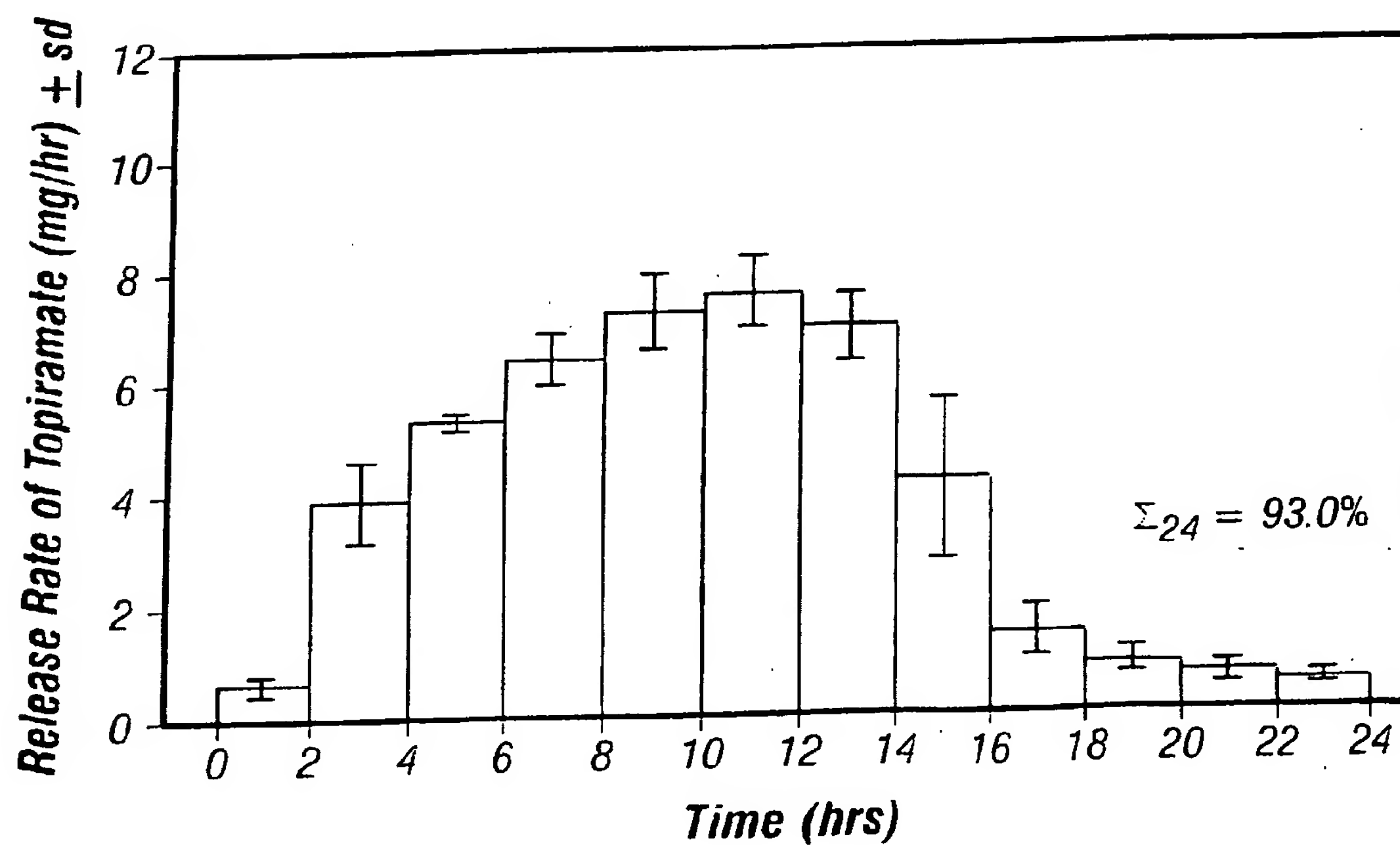


FIG. 9



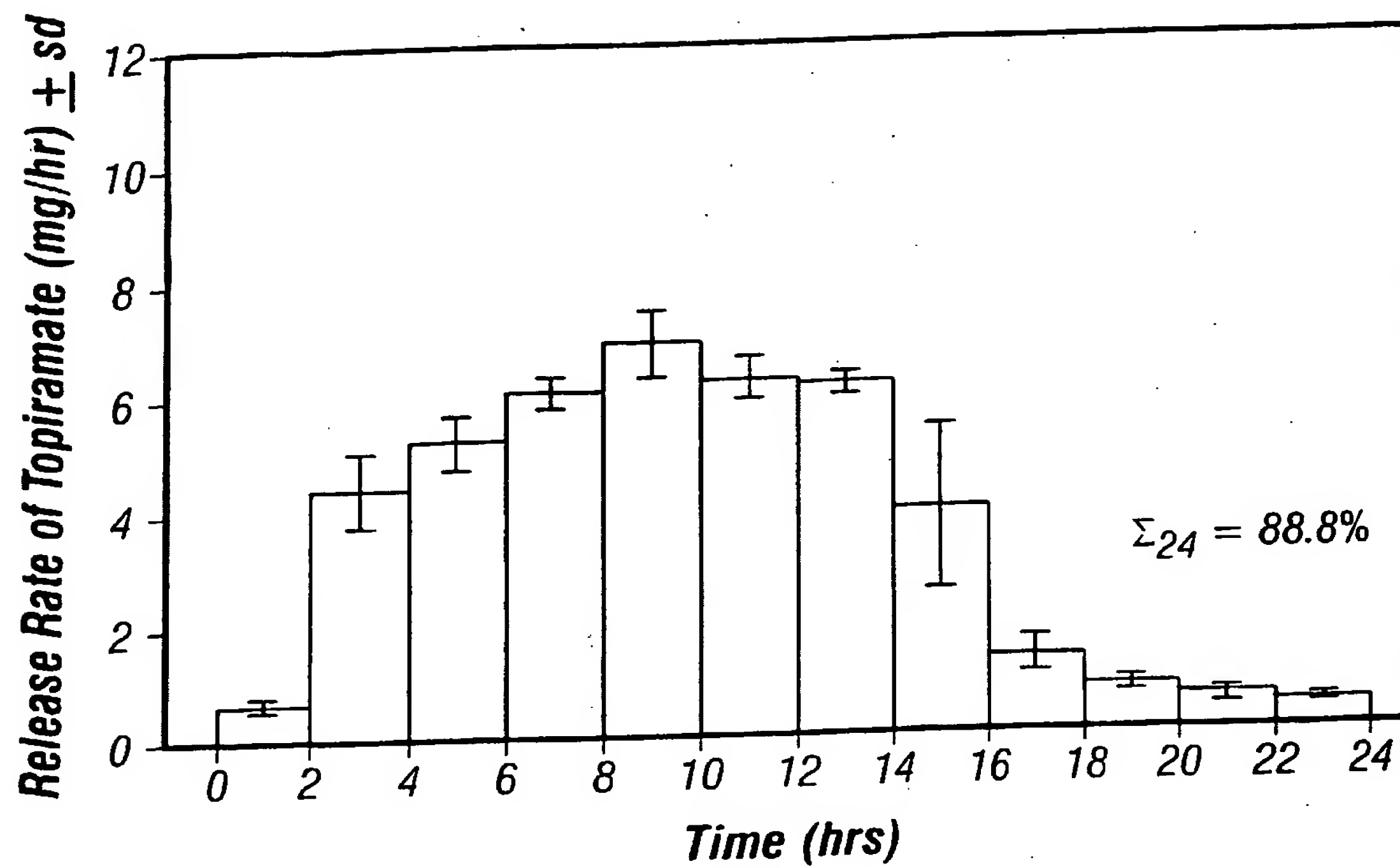


FIG. 10

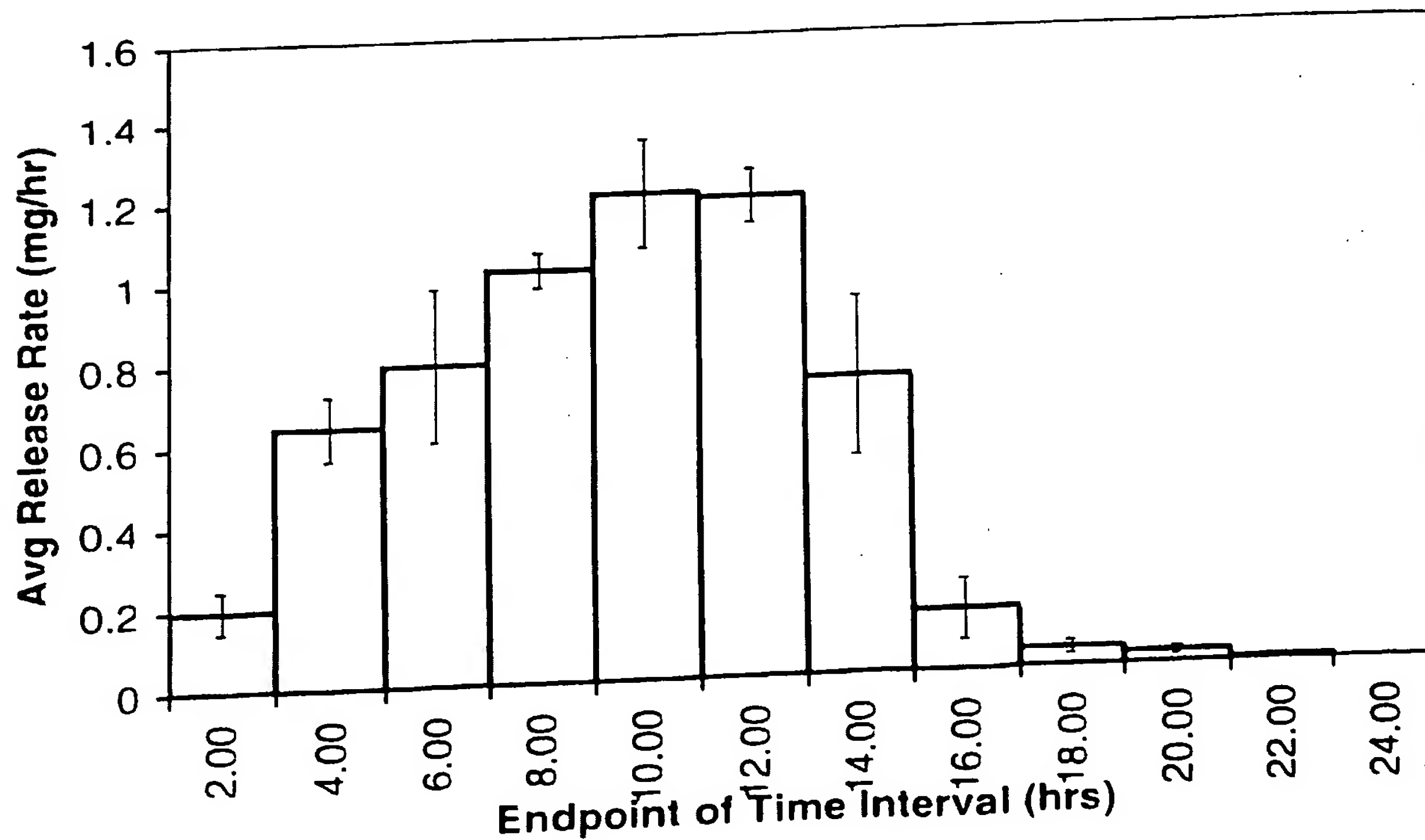


FIG. 11

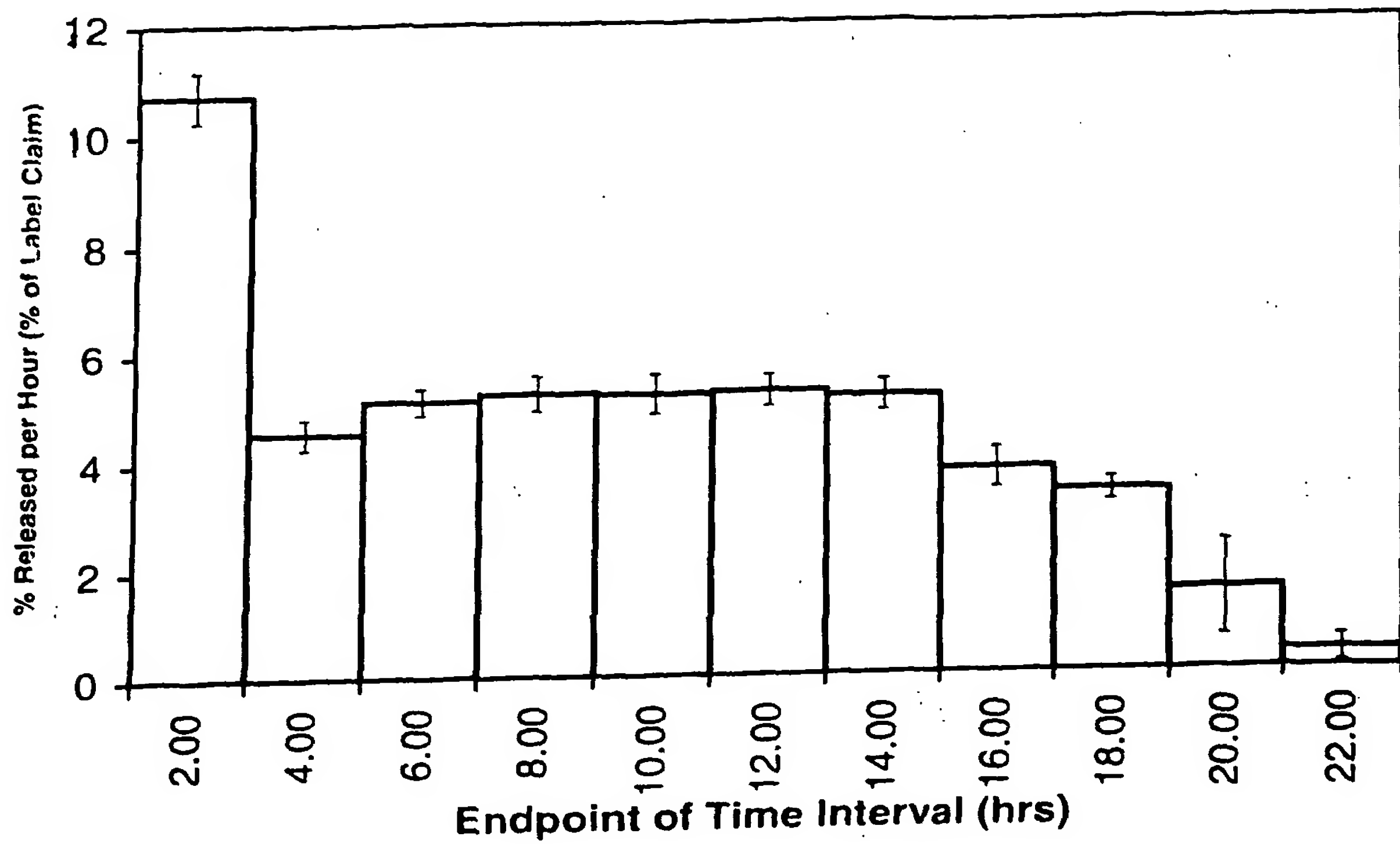


FIG. 12

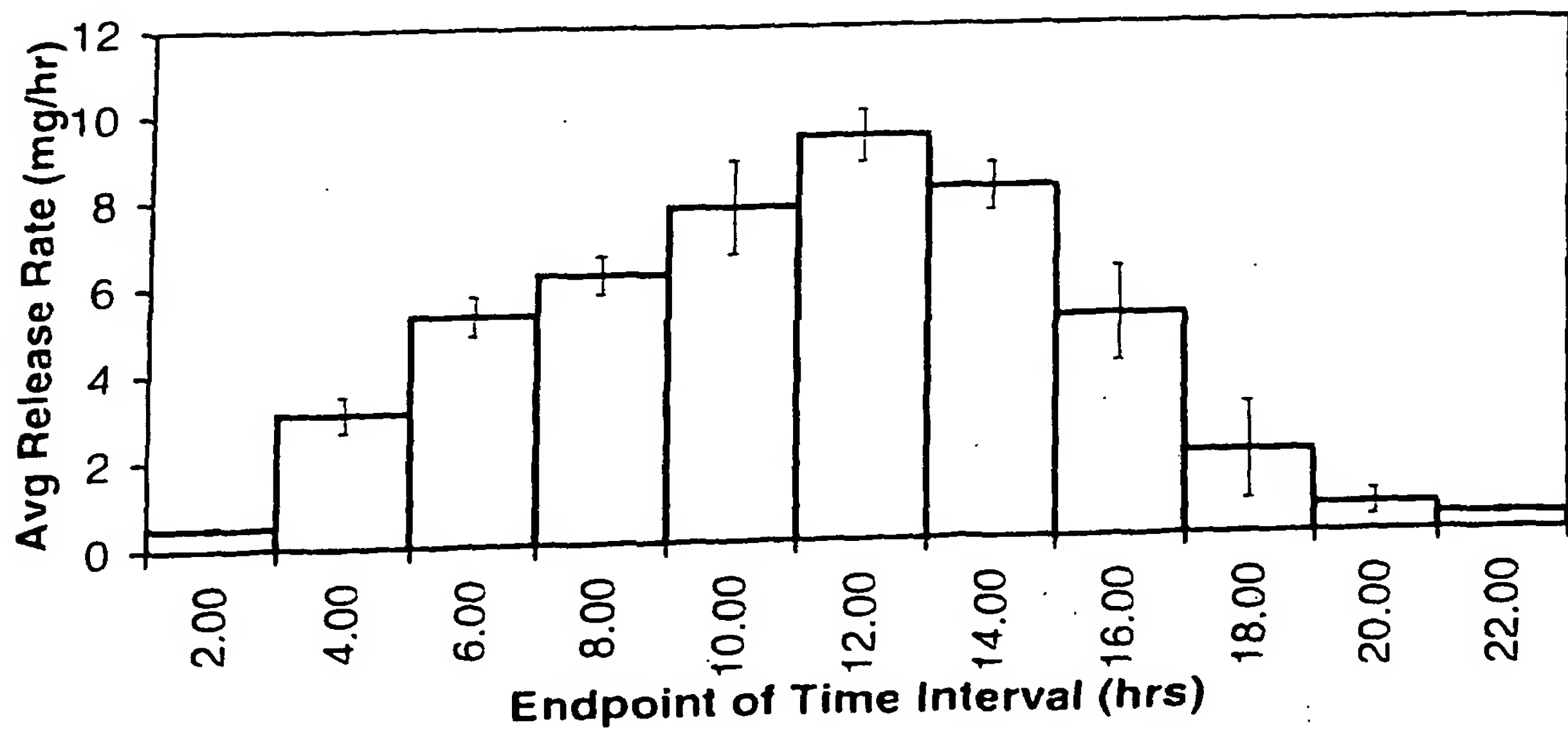


FIG. 13

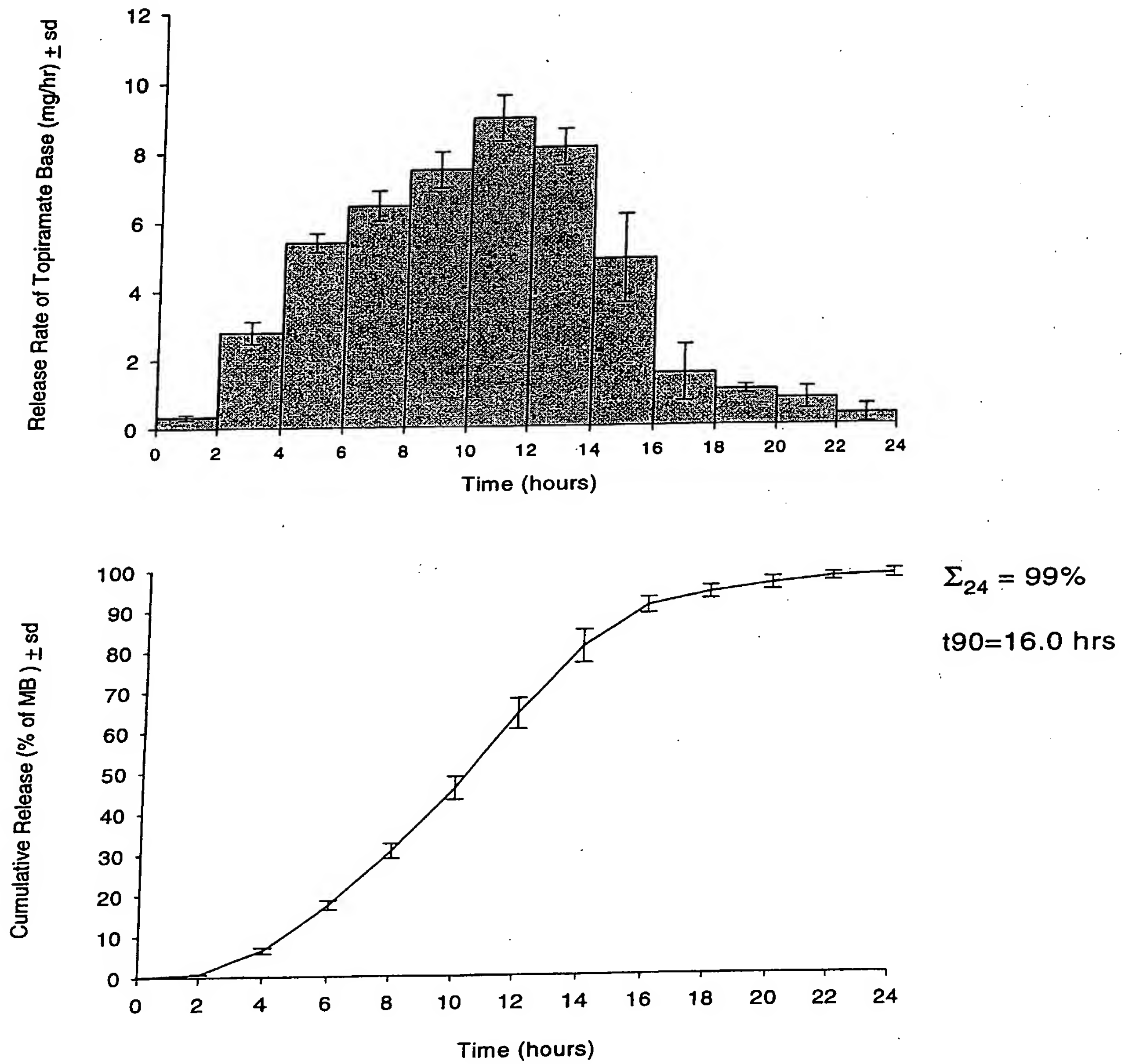


FIG. 14

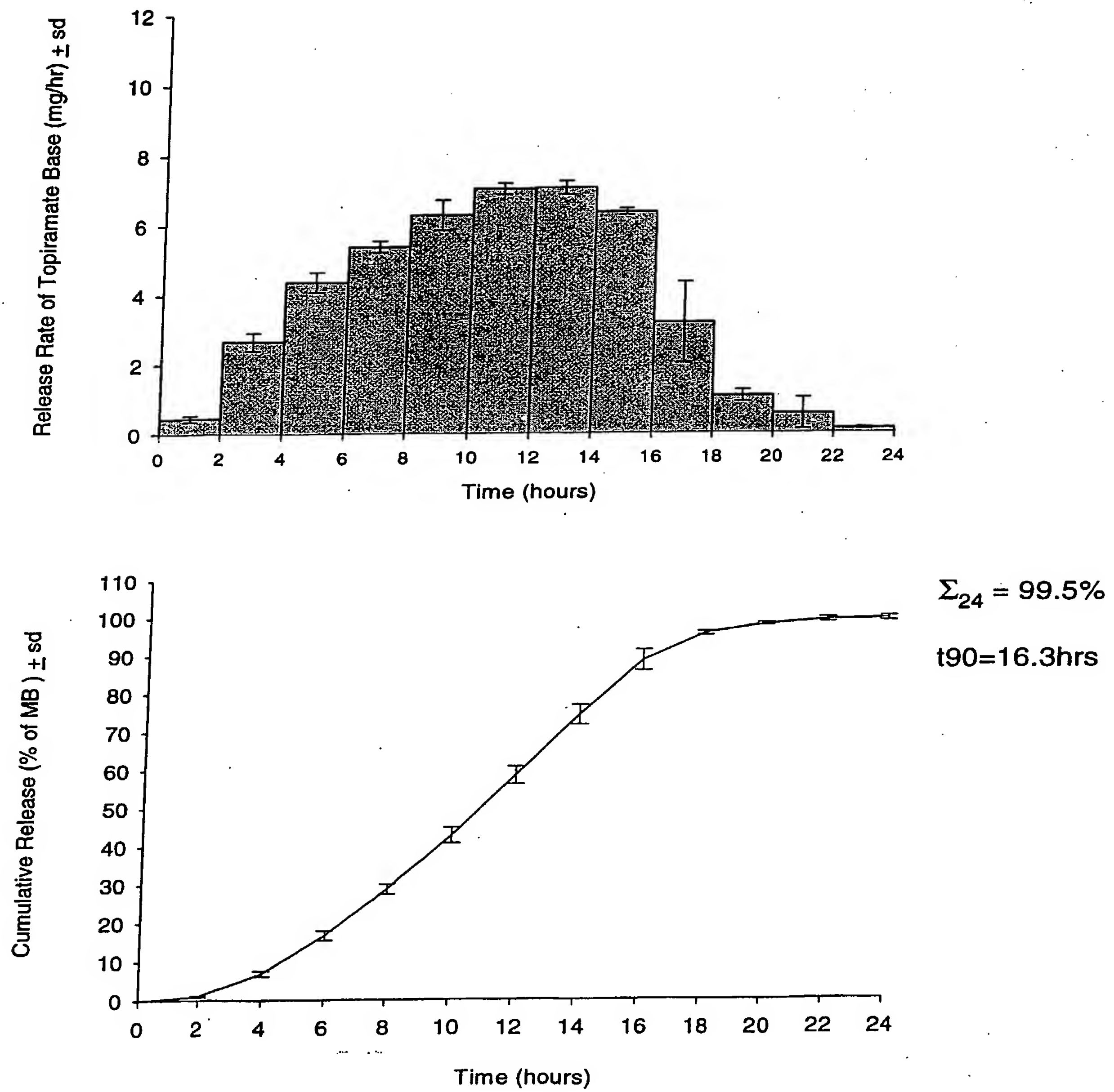


FIG. 15

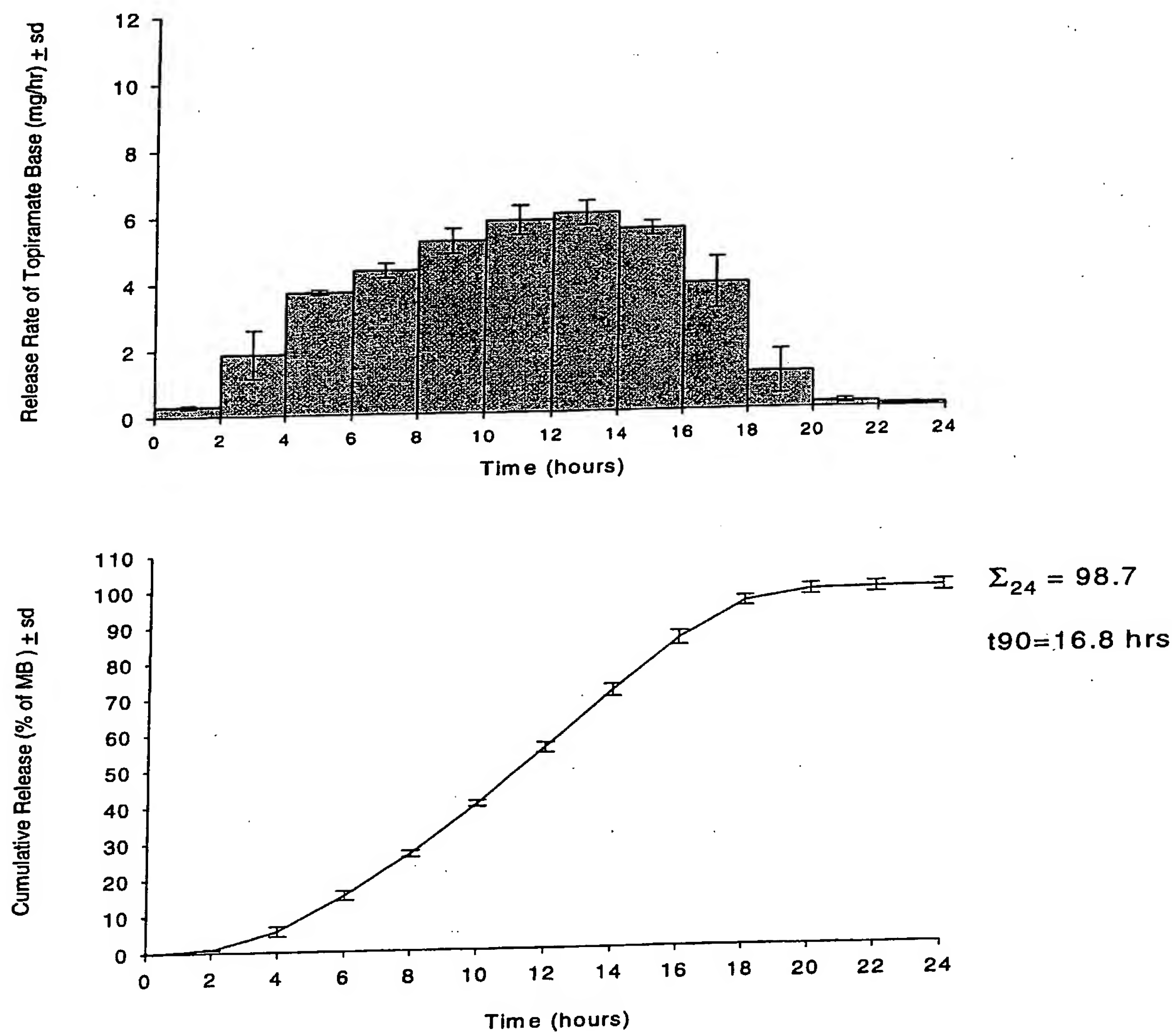


FIG. 16